X-REPORT BREAST: IT TOOLS TO EARLY DETECT BREAST CANCER THROUGH OPTICAL IMAGING

Dynamic Optical Breast Imaging, DOBI

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Abstract: Breast cancer is the second leading cause of cancer deaths in women today; according to the American Cancer Society, about 1.3 million women will be diagnosed with breast cancer annually worldwide and about 465,000 will die from this disease. In the western world, its incidence in females in premenopausal status results similar or superior to the incidence in females in postmenopausal status. Therefore, it is imperative to identify diagnostic tools able to detect breast cancer in young women from the very early stages. This paper presents an IT application developed to support Medical Doctors in diagnosing and reporting with an innovative non-radiating, non-invasive optically-based breast cancer detection system, suitable for scanning of young women. This system - ComfortScan - relies on a methodology – DOBI, Dynamic Optical Breast Imaging - based upon the use of a red monochromatic light beam and able to identify neoangiogenetic areas related to the onset of cancer. The application – X-Report Breast – interprets the images captured by ComfortScan and provides automatic reporting and diagnosis. X-Report Breast proves to be highly valuable in supporting the early diagnosis of breast cancers with ComfortScan, increasing the survival probability and diminishing the invasive surgical impacts.

1 INTRODUCTION

Breast cancer is the second leading cause of cancer deaths in women today (after lung cancer) and is the most common cancer among women, excluding non melanoma skin cancers. According to the American Cancer Society, about 1.3 million women will be diagnosed with breast cancer annually worldwide and about 465,000 will die from this disease. Breast cancer death rates have been dropping steadily since 1990, according to the Society, because of earlier detection and better treatments. However, breast cancer is dramatically growing in the western world: the lifetime probability of developing breast cancer in developed countries is about 4.8%, according to the American Cancer Society (the probability is about 13% for any type of cancer), while in developing countries is about 1.8%.

Today, the largest majority of this inauspicious events is diagnosed in females aged above 50, but the new female generations are exposed during their entire life to the phenomena responsible for the increase of the risk factors (environmental pollution, estrogens through food or pharmaceutical products, cigarette smoke); consequently the breast cancer incidence in females in premenopausal status already results similar or even superior to the incidence in females in postmenopausal status (Ferlay et al., 2004; American Cancer Society, 2005-2006) (Table 1).

Table 1: Probability to Develop Breast Cancer Within the Next 10 Years.

Probability of Developing Breast Cancer Within the Next 10 years	
By age 20	1 out of 1,985
By age 30	1 out of 229
By age 40	1 out of 68
By age 50	1 out of 37
By age 60	1 out of 26
By age 70	1 out of 24
Lifetime	1 out of 8

It is therefore imperative to decrease the age of the first breast scan, which calls for the adoption of long term riskless technologies, protocols and diagnostic methods. This paper presents an IT application purposely developed to ease and

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harmonize diagnosis and reporting in an innovative optically-based breast cancer detection system.

2 DIAGNOSTIC METHODS

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 deciding if the third step, a biopsy, is required (Nass et al., 2001).

Today, mammography is the most popular diagnostic tool, however it has two main drawbacks: (i) it is radiating, which can induce long term negative effects on young women; (ii) it is inefficient on dense breasts, which is typically the case for young women.

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. In fact, below age 50, the value of mammography screening is less clear (Eliceiri and Cheresh, 1998) because the greater density of breast tissue in younger, premenopausal women makes mammography results more difficult to interpret, reaching the 50% of false negative or positive reports.

Further investigation methods are breast ultrasound, MRI and PET.

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 it, nor detects very small tumors (Angiogenesis Foundation, 2001).

Theoretically speaking, Breast MRI (Magnetic Resonance Imaging) is a powerful imaging modality in anatomical and physiological detection But the drawback is that it is uncommon to use Breast MRI in screening or follow-up because of the timing, cost and sophisticated environment. Moreover, MRI cannot detect microcalcifications (National Cancer Institute, 2011).

Positron Emission Tomography (PET), that requires radioactive substance injection into the body, is an expensive and very invasive alternative.

Consequently, optical technology appears to offer the best perspectives as far as scanning of young women is concerned. Optical breast examination (Dynamic Optical Breast Imaging, DOBI) (Zhang et al.) is an innovative, non-invasive methodology based upon the use of a red monochromatic light beam. The DOBI method is a functional examination of the breast that aims to identify neoangiogenetic areas related to the onset of cancer.

The system based on DOBI – ComfortScan - is digital, operator-independent and easy-to-integrate with any other diagnostic systems; it allows quick, painless examinations and makes available new functional physiological data.

3 DOBI

DOBI is based upon the tissue deoxyemoglobin light absorption principle. Dynamic volumetric changes in blood and deoxyhemoglobin absorption changes are commonly found in malignant tumors and result in a unique angiogenic "signature." The DOBI method allows to measure these changes by applying mild uniform pressure to the breast. The change in pressure traps blood in the tortuous angiogenic structures that form around the tumor. This trapped blood becomes deoxygenated up to four times faster than normal tissue. ComfortScan, the DOBI-based system, 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 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.

3.1 ComfortScan Operation Principles

ComfortScan (Figure 1) is a system based on DOBI and designed to detect dynamic (physiologic) changes, increased blood volume levels and depleted oxygen levels (deoxygenated haemoglobin), that characterize malignancies. It consists of the following primary components:

Figure 1: The ComfortScan System.

Soft breast holder: a silicon membrane used to impress the necessary compression to the breast and achieve acceptable image contrast in the area of pathologic influence (API). Rise, fall and maintenance of pressure are managed and monitored by a custom-programmed microcontroller.

Breast platform with LED array: used both to hold the breast in the right position and to emit light in the single visible-red band through a flat-plane array of 127 light emitting diodes (LEDs). The custom programmed microprocessor precisely controls the optical exposure time and the intensity profile of the LED array.

Digital CCD camera, a high-gain, low-noise device used to capture the slight changes in light intensity within the illuminated breast.

System electronics and software to process the measured incremental changes by using a variety of subtraction and contrast enhancement techniques to produce the diagnostic functional image. A proprietary algorithm generates the breast angiogenic region unique vascular profile that stands out in marked contrast to other portions of the breast. By displaying a contrasting appearance, the system has the potential to confirm the suspect of cancer and differentiate cancer from both benign lesions and normal tissue within the breast, particularly matching this report with echograms, clinical findings, and also mammograms in over forty women. These images supply physicians with new information associated with cancer development.

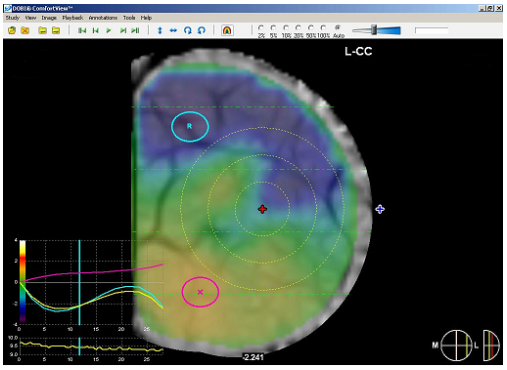

Figure 2: Comfortview Breast Chromatic Mapping.

Since vascular changes take place from the earliest stages of cancer development, the ability to image these changes can lead to earlier detection and, therefore, earlier treatment of developing cancers.

The dynamic analysis of the captured images is performed by means of a post-processing application – ComfortView- which provides a chromatic mapping, highlighting the zones of increased vascularisation (Figure 2).

ComfortView provides information about 4 main dynamic diagnostic parameters (Table 2) and several decision supporting parameters (Table 3).

Table 2: Main Assessment Criteria.

Main Assessment Criteria	
LOCATION	proximity to epicenter
SPATIAL	focal or diffuse lesion
TEMPORAL	downward trend and study as the software select the optimal contrast
CONTEXT	similar/dissimilar curve

Table 3: Secondary Assessment Criteria.

Secondary Assessment Criteria	
Margins	0 pt: non-assessable and indistinct; 2 pt: feathered; 4 pt: clearly defined and located
Diameter	0 pt: > 4 cm and not defined 1 pt: between 3 and 4 cm 3 pt: between 1 and 3 cm(well defined)
Distance from nipple	1 pt: non –assessable and distance < 1,5 cm 2 pt: between 1,5 and 3 4 pt: > 3 cm
Localization vs ROI	0 pt: external lesion 2 pt: inside 3rd ring 3 pt: inside 2nd ring 4 pt: inside 1st ring
Max saturation Intensity	2 pt : if < -2 4 pt : if between -2 and -4 6 pt : if > -4
Time for AIP to become violet	0 pt: never and > 20 sec 1 pt: between 10 and 20 sec 2 pt: if <10 sec
AIP Visualization time (sec)	0 pt: if < 10 sec 2 pt: between 10 and 20 sec 4 pt: if > 20 s.
I/T curve score (AUTO)	0 pt: non -assessable 1 pt(negative): positive only curve 2 pt(benign): mainly positive, fluctuating curve 3 pt(doubtful): fluctuating curve with both negative and positive values (slightly descending, curved shape) 6 pt(suspicious): rapidly descending (still curved shape) 9 pt(positive): rapidly descending , negative values (straight descending line)
I/T curve score (Range 10)	Same as previous (I/T curve score (AUTO))
I/T curve score (AUTO)	0 pt: non-assessable, indistinct, feathered, broadened 3 pt: well defined and centered on the lesion
AIP Curve score (similar/dissimilar)AUTO	0 pt: similar 3 pt: variable non clearly dissimilar 6 pt: dissimilar
AIP Curve score (similar/dissimilar) Range 10%	0 and 3 pt: as above (AIP Curve score AUTO) 6 pt: dissimilar(with increasing divergence)

Each parameter has a weight, represented by an associated value which depends upon its importance in the evaluation process (weighted score). The weighted sum of the values obtained for each considered parameter during an examination provides an overall score (called DOBI Level) which corresponds to a diagnosis, as reported in Table 4.

Table 4: DOBI Level.

DOBI Level	
DL 1	no actual signs of attenuation of the light beam
DL 2	no actual clearly abnormal signs of attenuation of the light beam
DL 3	actual attenuation of the minimally abnormal light beam
DL 4	actual attenuation of the abnormal and suspicious light beam
DL 5	actual attenuation of the clearly abnormal light beam

4 X-REPORT: AN IT TOOL TO SUPPORT DIAGNOSING

Although the dynamic analysis and the post processing activities are operator independent, the final step, represented by the valorization of each measured parameter, depends on the subjectivity of the Medical Doctors (MDs).

MDs with substantial DOBI experience produce completely similar diagnoses, often restricting the evaluation to the 4 main parameters. On the contrary, MDs with limited DOBI experience, which represent the large majority, may have slightly different interpretations, often due to their background and previous experiences. A large deployment of the DOBI diagnostic method cannot ignore this fact.

Moreover, having in mind the objective to extend the use of the DOBI method to screening, it is imperative to shorten the time to diagnose automating the valorization of the parameters, the calculation of the overall DOBI Level and the reporting.

Socrate Medical has developed an interpretation and reporting application software that, based upon interpretation rules agreed by a team of worldwide renown experts, allows to free the diagnostic process from operational factors, speed up and unify reporting procedures and presentation to patients.

This application, called X-Report Breast, has been developed in cooperation with the researchers of the Pascale Hospital in Naples (Italy) and validated by senior developers of ComfortScan in the USA.

X-Report breast has been developed building upon Socrate Medical's experience in reporting software for different medical sectors, mainly gynaecologists and obstetrics. The system is composed by the modules in Figure 3.

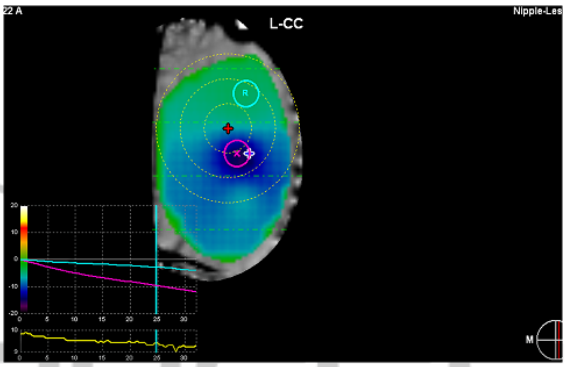

Figure 3: X-Report Flowchart.

The Execution block is where the automatic calculation process takes place. Within the calculation package, the numerical values and curve shapes obtained from the examination are compared with the standard values and shapes stored within the system. This permits to valorize each measured parameter, qualify (e.g. similar or dissimilar, Figure 4) and valorize the curves. Obtained values are summed and the overall result provides automatically the response based on DOBI Level as explained above and shown in Table 4.

All results are collected in a central data base and used to feedback and tune the weighted score system.

Although the X-report software and the working procedure are the same in all systems, the weighted scores may slightly differ, depending on environmental and feminine specific characteristics (e.g. skin color, average breast density and size, etc). The impact of these differences on the weighted score system has to be further investigated to define whether a unique classification can be uploaded or specific settings have to be foreseen.

X-Report Breast offers further investigation options to MD's: the Event/Visit block allows to compare subsequent visits in order to evaluate the progress or regression of the cancer.

The Lesion block allows, among other functions, to compare the right and left breasts against lesions. This feature is of paramount importance because symmetry of nodules and lesions is a strong positive indicator, able to exclude any malignancy with high probability.

Figure 4: Measured vs Standard Haemodynamic Response.

5 CLINICAL CASES

The experience built so far demonstrates that X-Report Breast is highly valuable to support MDs in early diagnosing breast cancers with ComfortScan.

In order to evaluate the effectiveness of the X-Report tool in assessing the DOBI Level criteria, all participant to the DOBI Group ethical committee institutes, are going to participate to the method evaluation, reporting the same 46 cases in double blinded. Results shown same DOBI Level classification thank to X-Report software tools.

First results on 113 women treated with X-Ray, US, DOBI and surgery demonstrated 80% sensitivity and 88% specificity using the cut off DOBI Level 30,5pt. Further evaluations are ongoing.

Other DOBI user results report that using X-Report software and the DOBI Level method high specificity, and high sensibility are obtained: both values are higher than 80%.

6 CONCLUSIONS AND FUTURE PLANS

Today, X-Report Breast is installed in all the ComfortScan systems deployed in Italy and offered as additional feature worldwide. The automatic DOBI Level calculation package will ease the work of the MDs, allowing non fully experienced MDs to use ComfortScan and make the diagnosing times compatible with the examination pace requested for screening.

The next steps will see the DOBI community to build a common reference data base where all worldwide available patient data will be stored and analyzed with the objective to draw conclusions of general validity and usefulness beyond the specific needs of X-report. This powerful tool will accelerate the acquisition of further experience on the impact of the assessment parameters, possibly suggesting reductions and/or simplifications of the present set.

It will also continue the comparison between results obtained through automatic diagnosing and human evaluation by senior MD's, with the objective to improve the assessment and valorization phases of the process.

X-Report Breast will be enriched with new features and functionalities to support these tasks.

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APPENDIX

Angiogenesis Definition

Angiogenesis is the key biological process that occurs into formation and growth of new blood vessels and it is necessary for reproduction, embryonic development and wound repair. The complex angiogenic process is maintained in careful balance by a variety of factors, but if this balance is tipped in favor of too much or too little angiogenesis, a variety of pathological conditions can be the result, in particular, the role of angiogenesis in breast cancer has been documented (Folkman, 1971).

The cells of an incipient tumor require constant nourishment and oxygen as well as a way to remove waste products. 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.