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Clinical approach with optical imaging instrument. Perspective analysis on 617 young females

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ABSTRACT

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Aim. The present perspective study sets out to determine the diagnostic accuracy of Dynamic Optical Breast Imaging (DOBI) in conjunction with ultrasound systems for the prevention, diagnosis and monitoring of breast cancer in young females by means of a non-invasive technology examination. This examination methodology can represent a methodical support in uncertain and particular neoplasms or an alternative approach to breast imaging especially for young women.

Methodologies and systems. This study was conducted on 617 young females aged 25-39 with clinical risk of developing a cancer or because of their breast density there is suspicion of breast cancer. Standard imaging – All patients were submitted to clinical investigation by means of both ultrasound (US) and dynamic optical breast imaging (DOBI). When both US and DOBI clinical results were positive for neoplasm, the second step consisted of a surgical biopsy. If only US or DOBI showed positive for neoplasm those patients were submitted to core biopsy. Imaging technique – Diffuse Optical Imaging using near infrared light (640 nm) and recording the reaction of breast tissue to a compression stimulus that induces change in blood flow.

Results. The dynamic optical imaging showed a statistical difference ($p<0.001$) in patient analyses compared with ultrasound. In this study, the dynamic optical breast imaging had a sensitivity equal to 98%.and a specificity to 87%.

Conclusion. This non-invasive, imaging-based methodology has a high potential for breast cancer prevention independent of breast size, density or hormonal status. It is particularly suitable for the younger female population whose breast tissue is

SOMMARIO

Studio clinico mediante dinamica ottica mammaria per immagini. Analisi prospettica in 617 donne con età inferiore a 40 anni.

Scopo. Questo studio prospettico mira a valutare la accuratezza diagnostica di due metodiche non invasive, DOBI (Dynamical Optical Breast Imaging) ed ecografia mammaria (US), a fini di prevenzione, diagnosi, monitoraggio del cancro della mammella in donne con età inferiore a 40 anni. Queste due metodiche potrebbero rappresentare una reale alternativa di supporto alle metodologie standard per la prevenzione del cancro della mammella specialmente in donne con seno denso e pertanto di difficile approccio diagnostico.

Sistemi e metodi. Questo studio ha analizzato 617 donne con età compresa tra i 25 e i 39 anni, elevato rischio per cancro della mammella o riscontro palpatorio di neoformazione mammaria. Le metodiche standard portate a corredo non sono state valutate in prima istanza in quanto tutte le pazienti sono state studiate mediante esame ecografico mammario associato a dinamica ottica mammaria. In caso vi fosse un riscontro di positività o di sospetto diagnostico in entrambe le metodiche, tutte le pazienti sono state sottoposte ad esame bioptico istologico incisionale. Nei casi di US/DOBI dissocianti, ma altamente sospetti, tutte le pazienti sono state sottoposte ad esame istologico con ago "tranciante".

Le immagini della tecnica DOBI vengono elaborate da microprocessori basandosi sull'utilizzo di luce monocromatica rossa a 640 nm che valuta la vascolarizzazione della ghiandola mammaria in relazione alla percentuale di desossiemoglobina e alle variazioni di flusso ematico indotte da micropressioni su tutta la mammella, partendo da 4.5 mmHg fino ad un massimo di 9-10 mmHg.

Risultati. La dinamica ottica per immagini mostra una differenza statisticamente significativa ($p<0.001$)

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more absorptive to radiation and therefore more difficult to image.

rispetto alle pazienti valutate solo con ecografia mammaria. In questo studio il DOBI raggiunge una sensibilità pari al 98% e specificità dell'87%.

Conclusioni. Questo studio ha valutato la bontà diagnostica associando due metodiche non invasive che hanno dimostrato una grande potenzialità per la prevenzione del cancro della mammella indipendentemente da densità o stato ormonale; in particolare, potrebbero essere di grande aiuto per la prevenzione in donne giovani con seno denso e ad elevato rischio.

Key words: breast cancer, non-invasive diagnosis, Dynamic Optical Breast Imaging (DOBI).

Parole chiave: tumore maligno mammario, diagnosi non invasiva, DOBI.

INTRODUCTION

Breast cancer is more common in the Western world than elsewhere. The great majority of cases are diagnosed in females aged above 50 year. In Italy alone in 2009 the number of breast cancer cases was 39,600 and statistically 7% of females have a clinically visible breast cancer.

All females will be exposed during their entire life to the phenomena that increase the risk factors. The result of this is that the incidence of breast cancer in females in premenopausal state is quite similar to incidence in females in postmenopausal state (1,2). In Italy it represent the first death cause in women aged between 35-50 years, corresponding to the 30,4% of population in women aged less than 44 yeas and 35,7% in women aged 44-65 years (3).

Generally tumours, breast cancer included, develop step-by-step over a period of time: many cellular alterations come together linked by a neo-angiogenetic process (4-8). This ensures a fertile developmental environment and a non-organic, uncontrolled, carcinogenic cellular proliferation (6,7). Contrary to this, the hereditary tumour linked to genetic deletions of BRCA1-2 genes represents a limited phenomenon (about 5-10 out of 100) in the breast cancer landscape and it is due to a hereditary genetic defect (15).

Today diagnostic breast imaging includes a number of different techniques and technologies including radiological mammography examination (MX) (8-10), supported by further examinations such as ultrasound scanning (US) of the breast. Other diagnostic technologies include Magnetic Resonance Imaging (MRI) (11), Positron Emission Tomography (PET) (8) and optical breast examination (Dynamic Optical Breast Imaging, DOBI – ComfortScan) (11). This latter – DOBI – is a non-invasive methodology based on the use an array of red monochromatic light emitting diodes (LED). The DOBI system is digital and easy-to-integrate with other diagnostic systems; it enables quick examination and generates new functional physiological data. DOBI is based upon the combined evolution of the neo-angiogenetic process and the development of the carcinogenic mass (the first stage in the cancer development process). In fact, it is based on elasticity analysis of blood vessels and absorption of oxygen, both are different in physiological or pathological tissue, and the combination of these factors determines a positive diagnosis. The DOBI Medical ComfortScan system detects on-off differences by evaluating light absorption when a slight external pressure is applied to the breast. As a result of this pressure dynamic analysis creates different dynamic signatures for normal areas, showing relatively normal vascularisations, or neo-angiogenetic areas (difference between malignant and benign lesions).

METHODOLOGIES AND SYSTEMS

This perspective study aims to evaluate the usage flexibility of the DOBI methodology (differentiated diagnosis between benign and malignant neoplasm, breast physiopathology variation and evaluation) on female patients compared with US methodolo-

gy that is the first step for diagnosis in young women.

This study has been carried out at the Centro Medico MonteRosa (CMM), Milan, Italy, on a total of 617 woman (consecutively from September 2008 to March 2010), age range 20-39, with an average age of 35±1.1 years. Approximately 50% of the patients were included in the training phase for the physician to investigate.

All patients with a high risk of breast cancer or manifested clinical evidence of palpable breast neoplasm were scanned. All patients with evidence of solid lesion or doubtful determination or for occasional breast control were scanned with the DOBI system and US breast examination and compared with histology.

In all study cases the anamnesis data were evaluated by collection into a purpose-built database and processed according to a specific protocol and method; the score system (12) ranks women in 3 categories according to low, medium or high risk (standardized statistics) to develop breast cancer.

After anamnesis and clinical examination, all patients were submitted to both breast US by a Kretz-Voluson 730 and additional DOBI examination, independently of any other supporting imaging files (in this specific case, MR or US from other Institutes or Hospitals). In case of a positive result from the DOBI examination surgical biopsy with histological test was performed. Following a positive US examination a core biopsy was performed, guided by DOBI with a marker of hyaluronic acid. In case of inconclusive findings, or different results from DOBI and US, all patients were submitted to core biopsy. In case of doubt from US or DOBI the patient will be recall for DOBI after 3 months.

The DOBI methodology utilizes the absorption of red light at 640nm by deoxyhaemoglobin and the analysis of blood vessel elasticity. During the diagnostic examination, the patient stands in front of the DOBI device with the breast resting on a panel that incorporates 127 LED's. The breast is held in position on the panel from above by a thin silicon membrane which exerts a pressure of about 10 mmHg. The light emitted by the LED's through the breast is detected by a highly sensitive CCD camera located over the membrane, while all the process is computer controlled.

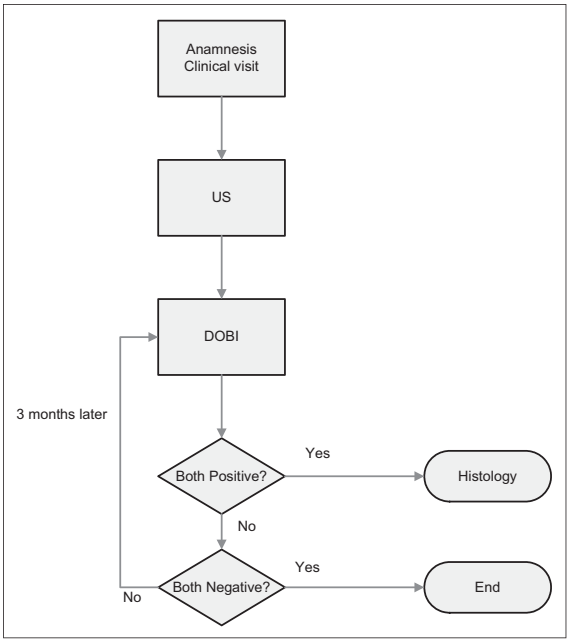

Figure 1. Study procedure description.

The recorded sequences of images are stored in a digital memory and post-processed to identify any minimal intensity variations between benign and malignant tissues.

The entire process is completed in under 10 minutes, which compares favourably with present alternative methodologies that take 2x to 3x longer. The immediately available results include a breast chromatic map together with a graphical representation of the post-processing results (see Fig. 2). This is expressed by a sinusoidal or linear curve with an associated positive or negative "Y" value resulting from the processing of an algebraic formula (5).

RESULTS

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 1 shows DOBI evaluation; Table 2 gives the results of evaluation by US conduct-

Table 1. DOBI evaluation.

Histology		Concordance DOBI	Discordance DOBI
benign	348	303 TN	45 FP
malignant	269	264 TP	5 FN
Sensitivity TP/TP+FN		98%	
Specificity TN/TN+FP		87%	

Table 2.

Histology		Concordance US	Discordance US
benign	348	246 TN	102 FP
malignant	269	201 TP	68 FN
Sensitivity TP/TP+FN		74%	
Specificity TN/TN+FP		70%	

ed before DOBI. For both types of study, data on sensitivity, specificity and chi-quadro= 62.38 ($p<0.001$) test have been calculated.

Breast cancer can have different pathological and oncological characteristics that are difficult to evaluate with standard methodology particularly in young women.

The use of DOBI and US combined examination has a statistical diagnostic accuracy higher then only US examination (72%).

In same case DOBI have correlated to 45 FP to histological examination, 36 patients have high or severe dysplasia with RR to develop in breast cancer same 3.3.

DISCUSSION

Today's most widely adopted diagnostic–preventative breast imaging methodology is mammography (2,8,10) with a sensitivity equal to 90% in palpable lesions and 60% in lesions smaller than 1cm. The lesions found in this study varied in size from 1.7mm. to 2.5cm. In the present study, the age of patients is 35±1.1 years. Generally, in this age range, the mammary glands show characteristics that make it difficult for the mammography examination to evaluate accurately the presence of very small parenchyma distortions; sensitivity is 67%, as reported by Kerlikowske (13), and this calls for an associated US examination. Unfortunately, this logical combination of examinations is not carried out in all medical centres. Moreover it is well known that the average US sensitivity is only 58-64%.

Clearly the diagnostic and therapeutic patterns must be more accurate if old and new methodologies are to work in synergy to effect a multidisciplinary approach (7,11).

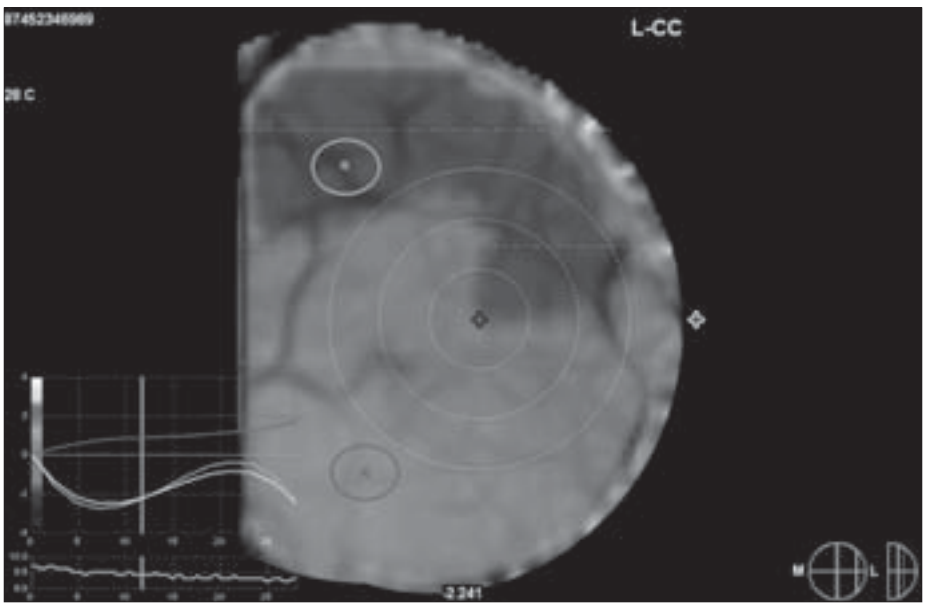

Figure 2. Example of chromatic map from ComfortScan.

This would need to be supported by a detailed and amplified cost analysis, whose aim is always to achieve more accurate diagnoses while reducing where possible the costs associated with biopsy. At present, the methodologies able to diagnose breast preclinic lesions are: MR (8,9), characterized by poor specificity (30-40%) but high sensitivity (98-100%) with a resolution up to 2mm (8), PET good sensitivity (77-90%) and good specificity (73%) (14) and DOBI, as shown in this paper with a high sensitivity (98%) and good specificity (78%).

After having carefully evaluated advantages, limits and the high sensitivity 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–preventative methodology, mainly for women with dense breasts where conventional mammography has poor sensitivity.

CONCLUSION

At present, DOBI (Fig. 3 – brand name "ComfortScan") proves to be a powerful system for diagnostic purposes in combination with traditional methodologies such as mammography and US, especially in cases of women with dense breasts and those at high risk from a clinical and anamnesis viewpoint where the first step in diagnosis is US. In particular, in young women the clinical and US 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 also be used for non-invasive monitoring.

Figure 3. ComfortScan.

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