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ARTICLE

# Optical mammography: a new technique for visualizing breast lesions in women presenting non palpable BIRADS 4–5 imaging findings: preliminary results with radiologic–pathologic correlation

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**Abstract**

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. Seventy-eight women consulting for non-palpable breast lesions were initially included in the study. 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. 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.

**Keywords:** *Near-infrared optical absorption imaging; breast.*

## Introduction

Breast cancer represents the second cause of cancer mortality in women, after lung cancer. Mammography is the gold standard imaging modality for the detection and characterization of breast tumours. Other imaging techniques used in conjunction with mammography and physical examination are mainly ultrasonography and magnetic resonance imaging. Computed tomography (CT) imaging and sestamibi scintimammography have been used in certain cases, but are not routinely performed[1].

A light imaging system that detects subtle physiological changes in tissues could provide a valuable adjunct to conventional modalities of breast imaging. In general, optical imaging can map tissue activity by means of low-intensity infrared light pulsed across the body part being imaged. A series of detectors record the amount of light reaching them and the time needed to pass through tissues. These measurements indicate the extent to which light has been scattered and absorbed. These values are subjected to changes according to the presence of oxygenated and deoxygenated blood. The data obtained can then be used to map oxygen supply and blood flow in the area of interest. Physiological information directly related to tumour vascularity and oxygenation can therefore be obtained, with inexpensive, non-ionizing and non-invasive instrumentation. The main features of this

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method are the spatial information – though limited by the diffuse light propagation – that takes advantage of the high contrast featured by blood vessels in the breast, and the spectral information that allows functional measurements of oxygenation, haemoglobin concentration, water and lipid content. Malignancies generally have a greater blood volume than benign tissue and elevated levels of deoxygenated blood[2]. Both of these markers can be detectable with optical imaging. When a single optical wavelength is used, the optical absorption, which is related to tumour angiogenesis, can be measured. Thus, this technique could possibly provide additional information on the detection and characterization of breast lesions with respect to the detection of hypervascularized, hypoxic tissue areas, strongly indicating the presence of an underlying malignancy. Breast MRI provides the same information but at a much higher cost.

This promising technique has been the subject of various studies. Optical imaging has been correlated with mammographic and ultrasonographic findings and pathological confrontation was obtained[3–6]. However, these studies were not particularly focused on optical imaging of non-palpable breast lesions.

Among the different types of optical imaging systems under experimentation nowadays, dynamic optical breast imaging represents an innovative method for detecting and characterizing vessels in breast lesions.

The purpose of this prospective study was to evaluate the diagnostic accuracy of this modality in women presenting non-palpable Breast Imaging Reporting and Data System (BIRADS) 4–5 lesions, using core biopsy or surgical specimen histology correlation. The feasibility of this technique has already been studied[7], so in this part of our study we focused mainly on the sensitivity and specificity of optical mammography.

## Materials and methods

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. Exclusion criteria were defined as follows:

- breast surgery or radiotherapy within a year of the potential optical scan date;
- breast core or excisional biopsy within the past 3 months;
- breast fine needle aspiration within 1 month;
- patients with small, firm breasts that cannot be properly positioned for the optical mammography (according to the judgment of the technologist performing the scan);
- patients having a change in hormone replacement therapy within the past 30 days;
- patients with sub-muscular breast implants, tattoos or piercing;
- patients with inflammatory breast or skin disease.

Written consent was obtained after patient information by the physicians.

Dynamic optical breast imaging was performed the same day and just before any interventional procedure scheduled in our department, whether this was a core biopsy or a pre-operative wire-hook localization. The procedure was as follows: the breast was placed and compressed in the craniocaudal position. A soft-hold membrane exerted a uniform pressure (10 mmHg) onto the breast, in order to better dissociate normal from abnormal, non-elastic vascular stroma. According to the literature, compression-induced changes in breast physiological properties are significant and should be accounted for when performing optical breast imaging[8]. Near infrared light was emitted in the 640 nm range by means of 127 light emitting diodes (LED) and was scattered and diffused throughout the breast tissue. LED adjustment, in order to obtain a maximum light intensity in the area of interest, was based on lesion localization according to mammographic and/or ultrasonographic findings. A cursor drawn from the nipple marked the area of interest. This adjustment permitted an optimal infrared light emission and absorption. A camera system captured the signal from the breast surface in order to acquire digital images of the breast during the scanning process (pixel size 0.4763 mm). Several images per second were recorded via this CCD camera for approximately 45 s and were used for dynamic curve calculation by means of a dedicated software-installed unit that was used for further image treatment (Fig. 1). The total procedure time was 70 s. All patients reported that it was a well-tolerated procedure.

At the end of the dynamic optical scan acquisition, three different types of images were displayed in the software unit screen (Fig. 2): from upper right to upper left, the first image in gray scale corresponded to the "mask" image, displaying vessel distribution into the

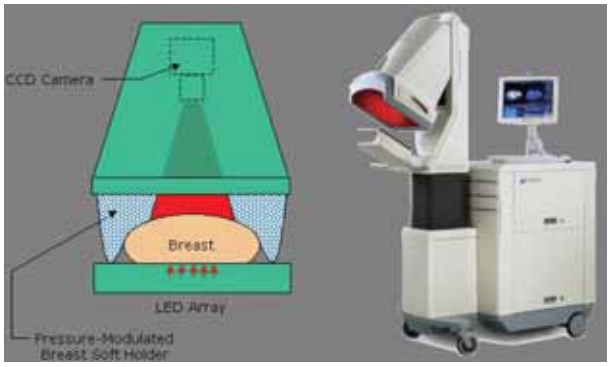


***Figure 1*** **The optical mammography unit consists of a breast-holder plate with integrated light-emission diodes (LEDs), a camera, and a software-image treatment system.**

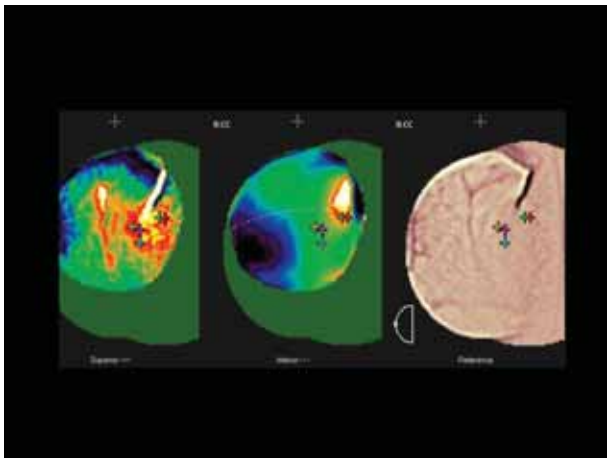

*Figure 2* **The three-level presentation of optical acquisition images allows a tomographic vision of superior (upper left image) and inferior (middle image) quadrants. The upper right image is used as anatomic reference, displaying major vessels inside the breast.**

breast, the middle one in colour scale represented the lower half of the breast and the right one, also in colour scale, represented the upper half of the breast. Light absorption varied according to the haemoglobin/deoxyhaemoglobin ratio thus permitting an evaluation of the vascularity status of underlying breast lesions.

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:

$$\mathrm{LOS} = (2 \times P) + (2.5 \times S) + (0.5 \times I) - \frac{A}{50}$$

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.

## Results

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.

Case 1 shows a typical BIRADS 5 lesion for which dynamic optical imaging was also positive: mammography depicted a spiculated opacity with irregular borders (Fig. 3a) corresponding to a hypoechoic, irregular nodule at ultrasonography (Fig. 3b). Dynamic optical acquisition was strongly suggestive of an underlying malignancy, detecting a blue-coloured, hypoxic area with negative dynamic curves (Fig. 3c). This lesion was found to correspond to an invasive ductal carcinoma at histology.

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. Case 2 corresponds to a radial scar, seen in mammography as an architectural distortion of the inner breast quadrants (Fig. 4a). 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 (Fig. 4b). Interpretation of the optical images indicated a probably benign breast lesion.

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

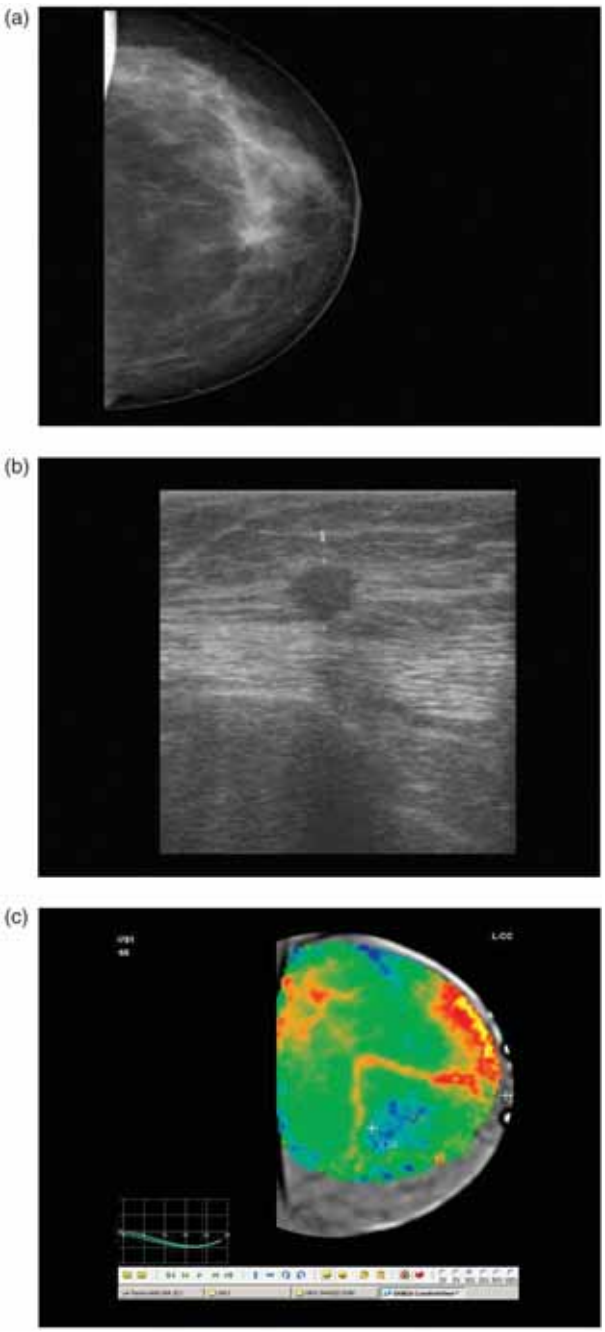


*Figure 3* **Case 1. (a) Mammographic images in craniocaudal view clearly depict a stellated lesion classified as BIRADS 5, with a high suspicion of malignancy. (b) High-resolution ultrasonography with a 10 mHz probe shows that the mammographic lesion corresponds to a hypoechoic, irregular nodule, BIRADS 5. (c) Dynamic optical imaging shows that the corresponding area of interest is highly hypoxic, with negative down slope dynamic curves, that strongly suggest an underlying malignant lesion.**

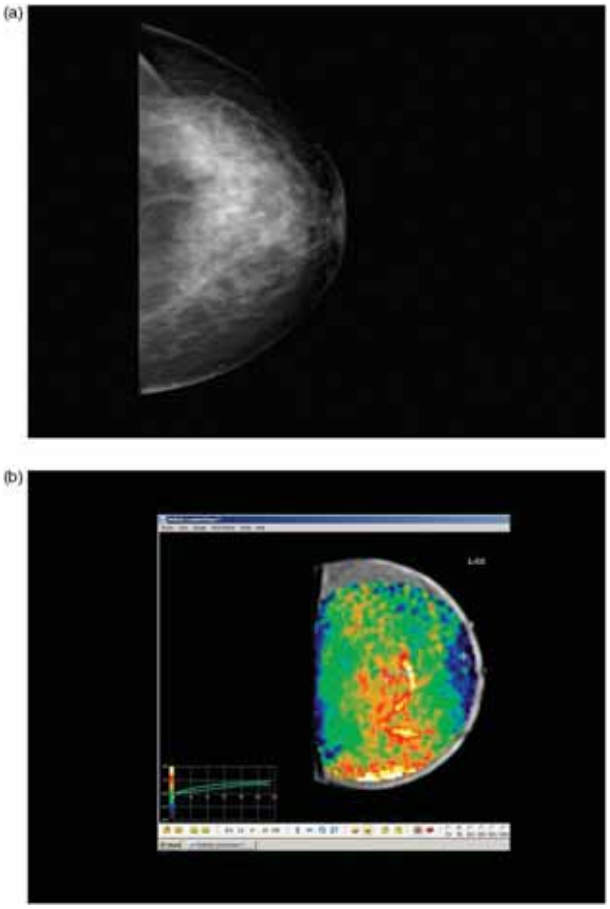


*Figure 4* **Case 2. (a) Mammography craniocaudal view depicts an architectural distortion in the inner breast quadrants, classified as BIRADS 4. The diagnosis of radial scar, or otherwise "Aschoff's" lesion was advocated. All these cases were subject to surgical excision, due to the high percentage of associated carcinomas, usually of tubular subtype. In this case histology was a simple radial scar. (b) Optical mammography was positive, detecting an early red blush, in agreement with a proliferative underlying pathology but without significant hypoxia, as is usually seen in benign breast lesions.**

(11 out of 19) corresponded to DCIS of small size (calcifications did not exceed 10 mm) and of low or intermediate grade. Ductal carcinoma in situ was difficult to detect by optical imaging, even when high filter resolution was applied; case 3 shows the mammographic findings of a DCIS presented as clustered, irregular microcalcifications in the outer breast quadrant (Fig. 5a). The corresponding optical acquisition (Fig. 5b) shows that no particular signal was emitted in the area of interest. Eight infiltrating carcinomas remained undetected by optical imaging; these were small size lesions, their diameter as measured at mammography or ultrasonography did not exceed 9–10 mm and they all corresponded to grade I lesions at pathology.

On a total of 72 patients we experienced 11 false positive cases and 19 false negative cases. Consequently, overall sensibility and specificity were 73% and 38%, respectively (Fig. 6). Sensitivity did not appear to be significantly affected by breast density.

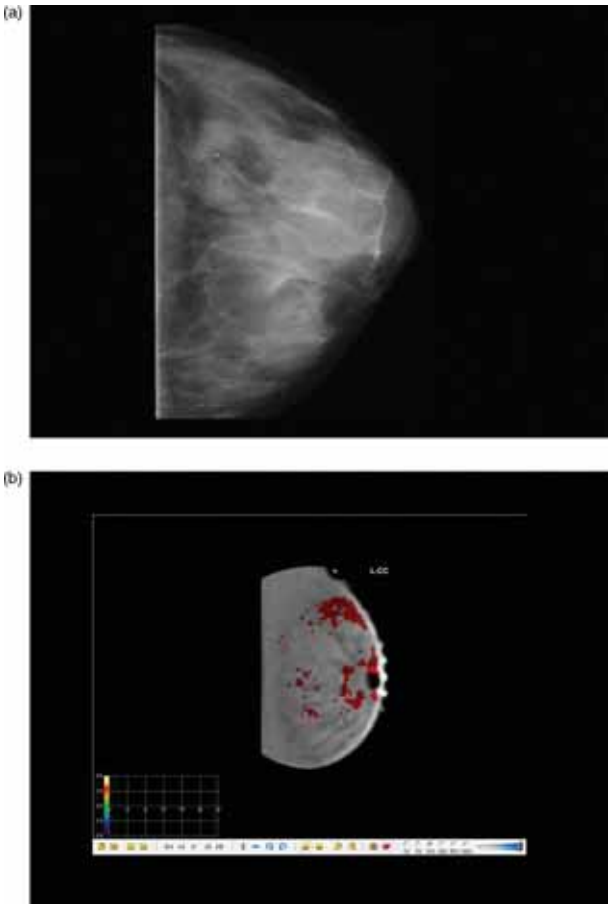


*Figure 5* **Case 3. (a) Craniocaudal mammographic view showing clustered, rather irregular, microcalcifications in the upper outer breast quadrant, classified as BIRADS 4 lesion. Histology was intraductal carcinoma. (b) False-negative findings during dynamic optical acquisition (shown here after high filter application). No signal detected in the corresponding area.**

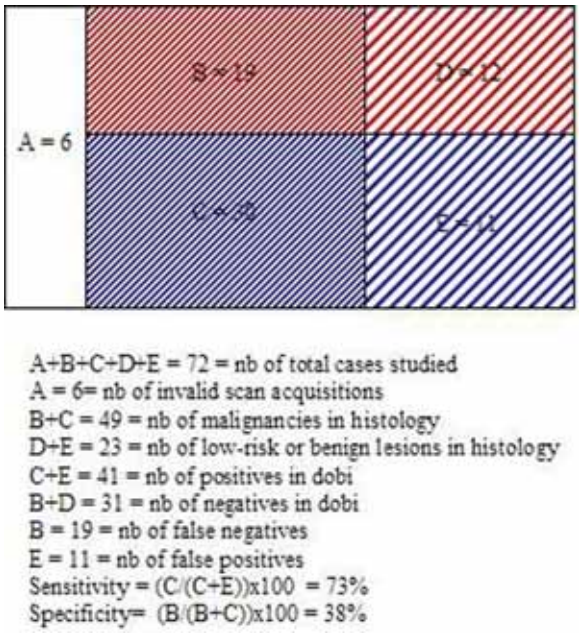


*Figure 6* **Table of sensitivity and specificity for a total of 72 lesions.**

## Discussion

Tumour molecular biology includes the vascular growth factors that are responsible for the development of abnormal tumoural vascular stroma. Neo-angiogenesis has been one of the hallmarks of tumoural activity and reflects closely the current molecular stage and potential aggressiveness of malignant lesions[11,12]. Imaging of neo-angiogenesis implies mainly invasive radiological procedures such as percutaneous arteriography after peripheral vessel catheterization, or computed tomography and magnetic resonance imaging angiography after intravenous administration of appropriate contrast media (iodine or gadolinium, respectively). In addition, in all cases a contrast medium has to be used, a peripheral venous approach has to be employed, not to mention the irradiation, the cost of the examination and the various contra-indications such as allergy or claustrophobia, resulting in sub-optimal performance of these techniques.

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[13–15]. 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[16] or magnetic resonance imaging[17]. 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.

Infiltrating carcinomas were easier to detect if larger than 1 cm in size. In the majority of cases, the light absorption signal was larger than tumour size as measured in conventional imaging modalities (mammography or ultrasonography). This was attributed either to light scattering or to inflammatory-reactional hypervascularization of breast tissue adjacent to the tumour. We did experience a case (Fig. 7) where mammography was unremarkable, and ultrasonography depicted a non-specific, hypoechogenic, micro-lobulated lesion initially diagnosed as cystic-complex lesion. However, this lesion was found to be suspicious at optical mammography, displaying a down slope negative dynamic curve. Biopsy under ultrasonographic guidance revealed lobular infiltrating carcinoma. Lobular malignancies are known to be occult lesions, difficult to diagnose in mammographic controls due to their particular pattern of spread into the adjacent tissues. In this case optical imaging was of particular interest for raising suspicion of an otherwise undetermined, purely ultrasonographic lesion.

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[18]. Further studies and continuous system improvement are necessary for a better evaluation and clinical application of this innovative method.

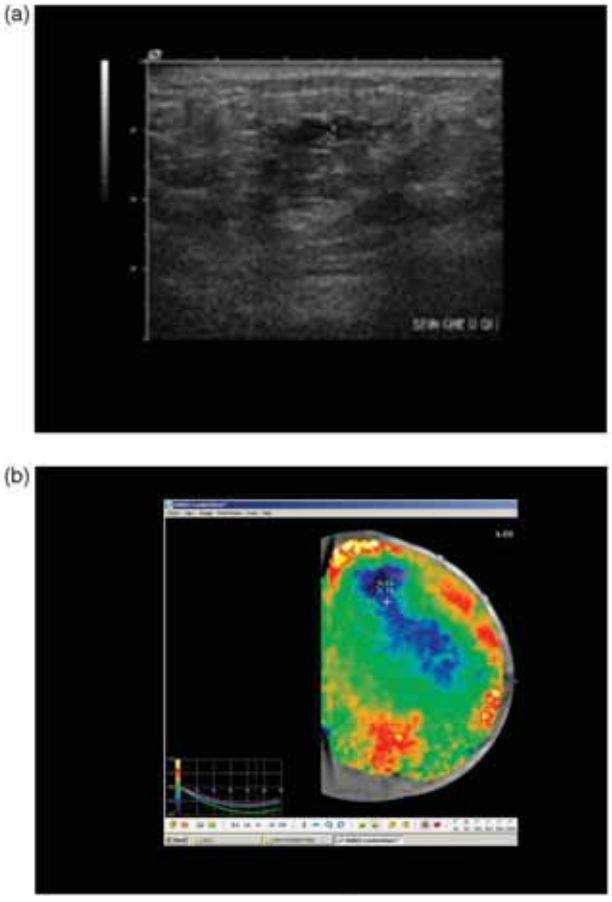


***Figure 7*** **Case 4. (a) Breast ultrasound with a 10 mHz probe depicts a hypoechoic micro-lobulated nodular lesion in a woman presenting with metastatic axillary lymphadenopathy and negative mammography. This lesion was initially considered as clustered micro-cysts. (b) Dynamic optical mammography reveals a highly hypoxic blue area with negative curves, corresponding to the ultrasound lesion localization. Biopsy under ultrasound guidance revealed infiltrating lobular carcinoma.**

## Conclusion

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.

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