Breast imaging using the Twente Photoacoustic Mammoscope (PAM): new clinical measurements

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ABSTRACT

Worldwide, yearly about 450,000 women die from the consequences of breast cancer. Current imaging modalities are not optimal in discriminating benign from malignant tissue. Visualizing the malignancy-associated increased hemoglobin concentration might significantly improve early diagnosis of breast cancer. Since photoacoustic imaging can visualize hemoglobin in tissue with optical contrast and ultrasound-like resolution, it is potentially an ideal method for early breast cancer imaging.

The Twente Photoacoustic Mammoscope (PAM) has been developed specifically for breast imaging. Recently, a large clinical study has been started in the Medisch Spectrum Twente in Oldenzaal using PAM. In PAM, the breast is slightly compressed between a window for laser light illumination and a flat array ultrasound detector. The measurements are performed using a Q-switched Nd:YAG laser, pulsed at 1064 nm and a 1 MHz unfocused ultrasound detector array. Three-dimensional data are reconstructed using a delay and sum reconstruction algorithm. Those reconstructed images are compared with conventional imaging and histopathology. In the first phase of the study 12 patients with a malignant lesion and 2 patients with a benign cyst have been measured. The results are used to guide developments in photoacoustic mammography in order to pave the way towards an optimal technique for early diagnosis of breast cancer.

Keywords: photoacoustic imaging, mammography, breast cancer, near-infrared light, ultrasound, optical imaging, angiogenesis

1. INTRODUCTION

1.1 Background

Worldwide, every year more than 1,300,000 women are diagnosed with breast cancer and annually, about 450,000 women die from this disease[1]. The imaging modalities that are mostly used for screening and diagnostic purposes are X-ray mammography (XRM) and ultrasonography (US). These modalities visualize anatomic features of breast tissue in order to discriminate malignant from benign tissue. However, both in screening and diagnostic imaging programs, breast cancers are regularly missed or often falsely detected[2].

For a breast tumor to develop and grow, certain functional changes to breast tissue are required. Those functional changes occur well before any morphologic alterations are visible on conventional XRM or US[3]. Therefore, focusing on

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functional changes in addition to the morphologic changes might improve the discriminative power of breast imaging. One example of such a change is caused by angiogenesis, which results in the increased vascularization that is required for a malignancy to grow[4].

This angiogenic phenomenon associated with tumor growth has implications for detection and diagnosis of tumors using near infrared (NIR) light. Diffuse Optical Tomography (DOT) and Diffuse Optical Spectroscopy (DOS) measure wavelength dependent tissue optical absorption and scattering coefficients. The absorption properties of light at the NIR wavelengths can give information about the blood dynamics, total hemoglobin concentration, tissue blood oxygen saturation and concentration of water and lipids[5]. In this way, information about the local vasculature and therefore about the presence of a breast malignancy can be obtained[6]. The greatest strength of the optical imaging techniques is that, because they are largely based upon concentration variations in blood and water relative to the surrounding tissue, one of the highest intrinsic biological contrasts possible can be achieved[7]. A major disadvantage is that the optical mammography techniques have a low spatial resolution. Due to the scattering properties of the NIR light, these techniques can only be used to image with an appropriate resolution at positions that are relatively superficial to the skin surface[7].

A technique that can combine a high optical contrast with a good resolution is photoacoustic imaging (PAI). With PAI, laser light in the NIR region is used for imaging, like in optical imaging. The optical absorption of the pulsed laser light causes a local thermal expansion, which in turn produces pressure transients in the diagnostic ultrasound frequency regime. This ultrasound propagates with minimal distortion to the surface where it can be detected using appropriate wideband ultrasound detectors. The time-of-flight, amplitude and peak to peak time of the photoacoustic signal depend on the amount of absorption of the laser light and on the size and position of the absorbing objects[8]. Those aspects are strongly determined by the local amount of vascularization. Because the detected signal is not the highly scattered light, but the much less scattered ultrasound, the resolution of PAI is superior to the optical resolution. PAI can combine optical contrast with the resolution of ultrasound, without magnetic compatibility problems, and without the use of contrast agents or ionizing radiation[9-10].

In the Biomedical Photonic Imaging Group (BMPI) of the University of Twente (UT) we have worked to develop photoacoustic imaging to address the limitations and drawbacks of the current technologies for breast imaging[11]. In 2007, the BMPI group reported their first results of NIR photoacoustic imaging of breast cancer in human subjects using the Twente Photoacoustic Mammoscope (PAM)[12]. It was possible to get five technical acceptable measurements on patients with breast malignancies (and on an additional one with a cyst). Of those, four cases revealed a higher photoacoustic contrast associated with tumor related vasculature[12]. These results demonstrated that NIR photoacoustic imaging has potential in the diagnosis of breast cancer but that improvements to the study protocol should be made in order to get the appropriate information.

1.2 New clinical study

In December 2010, a new clinical study has been started at the Center for Breast Care of the Medisch Spectrum Twente (MST) in Oldenzaal. In this study, up to 100 patients will be measured within a period of 1.5 years. Patients are measured within the normal diagnostic path at the Center for Breast Care, in between conventional radiology (XRM and US exams) and the ultrasound guided biopsy. The study can be divided into three phases and for each phase patients are included based on the suspiciousness of their lesion. In the first phase of the study, the focus is on a small number of patients with lesions that are highly suspicious for malignancy. The goal of this part of the study is to optimize the imaging methods for the visualization of malignancies. In phase 2 of the study, a large number of patients with lesions that are suspicious for malignancy are measured in order to define the photoacoustic markers that are indicative for the presence of a malignancy. In the last phase of the study, the absence of those photoacoustic malignancy markers will be verified in subjects with either healthy breast tissue or with benign lesions. Figure 1 gives an overview of the different study phases.

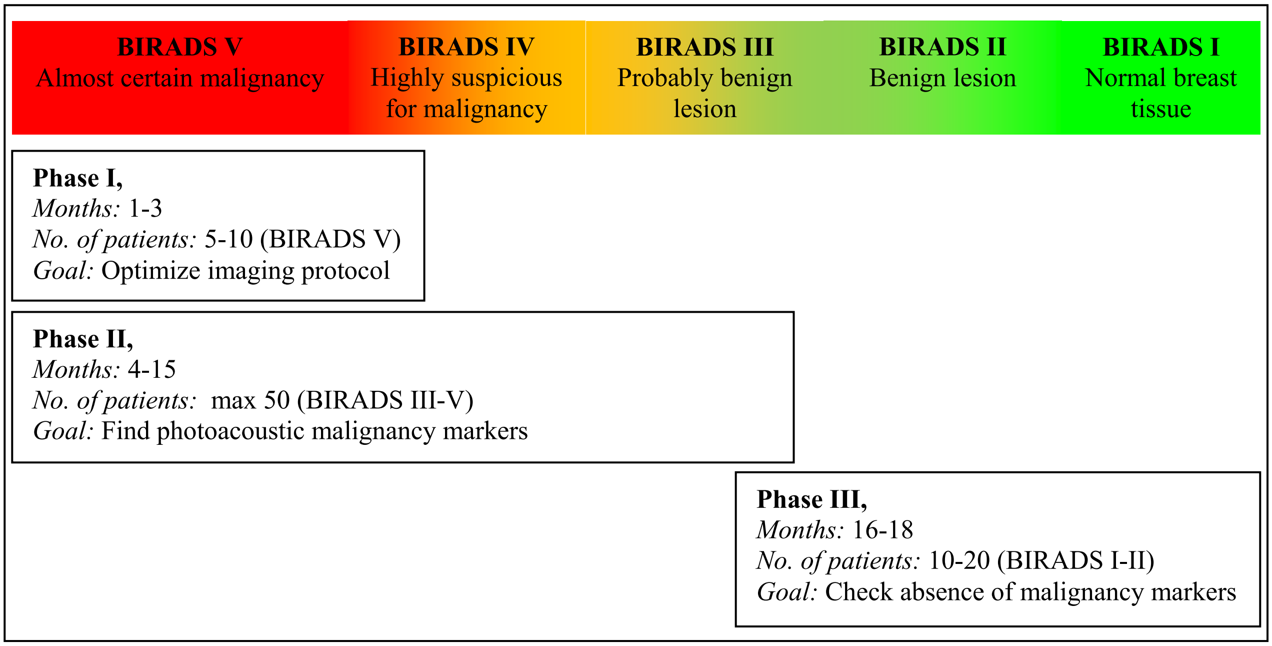

Figure 1: Overview of the patient study using the Twente Photoacoustic Mammoscope. Patients are included based on the BIRADS (Breast Imaging Reporting and Data System) classification of their lesion.

2. MATERIALS AND METHODS

2.1 Patient enrollment

Patients were included from the Center for Breast Care of the Medisch Spectrum Twente in Oldenzaal. Between December 2010 and April 2011, female patients with a palpable breast lesion that was judged as being highly suspicious for malignancy based on conventional radiology, were asked for cooperation to the study.

All patients had to sign an informed consent form prior to the study. The medical ethical review board of the Medisch Spectrum Twente has approved the study protocol and informed consent procedure.

2.2 Measurements

Patients were measured with the Twente Photoacoustic Mammoscope (PAM, Figure 2). The patient lay in a prone position on the bed with her breast pendant through the hole in the bed. The breast was slightly compressed between a glass plate for laser light illumination and a planar ultrasound detector. This configuration ensured a good acoustic contact between the breast and the detector. The breast was illuminated with a Q-switched Nd:YAG laser (Continuum Surelite, California), pulsed at 1064 nm (10 ns pulse duration, 10 Hz repetition rate). With a laser fluence below 30 mJ/cm^2 at the skin, the MPE guidelines for laser safety were fulfilled. The photoacoustic signals that were generated upon absorption of the light were detected with a planar, 1 MHz, unfocused ultrasound transducer (Lunar Corporation, Wisconsin) that consists of 590 elements. Each of those detector elements was activated one at a time. In order to scan a region of interest of the breast, the light delivery system moved in both vertical and horizontal directions. For each position of the light delivery system, the opposite detector element was activated and 90 averages were taken.

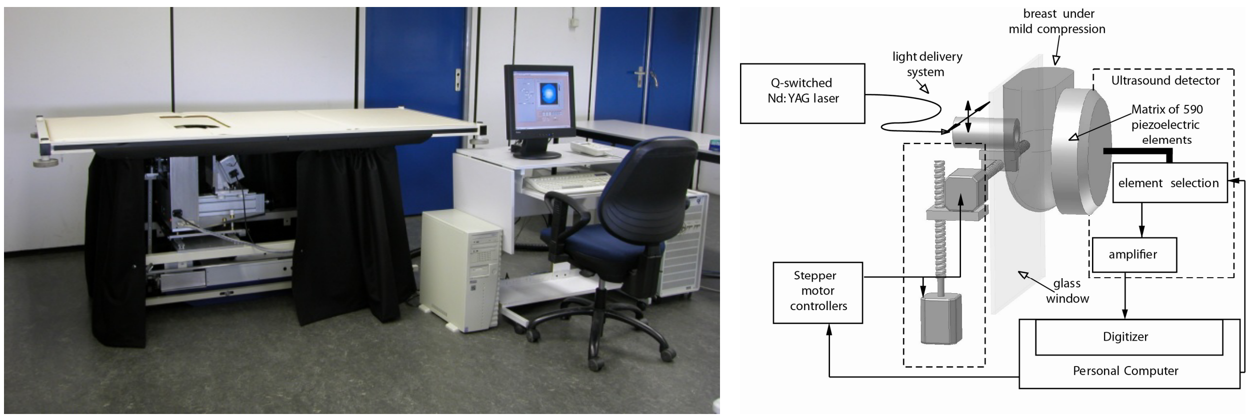

Figure 2: PAM hospital bed (left [12]) and a more detailed schematic of the equipment (right[13])

2.3 Data handling

The signals were reconstructed offline with a delay and sum reconstruction algorithm. In this algorithm, a sliding window operates on each acquired signal. The position of this window is determined by the distance between the voxel to be reconstructed and the specific detector element, assuming a constant speed of sound within the breast. Within this window, the peak-to-peak value of the signal is determined. The peak-to-peak values for all relevant elements are summed up and then assigned to the voxel, taking into account the directivity of the detector elements.

All voxel intensity values were scaled to the maximum value of the reconstructed volume. The resulting image volumes were compared to X-ray, ultrasound, and if available MRI images. Regions with high contrast were analyzed for their size and contrast with respect to the background. High and moderate contrast regions were defined as regions in which the intensity value of all pixels was more than 50 or 25% of the maximum intensity value within that specific slice respectively. The signal-to-noise ratio (SNR) of such a region was calculated via: $SNR=A_{lesion}/A_{background}$. In which SNR is the signal to noise ratio for the specific lesion, A_{lesion} is the mean pixel value within the lesion and $A_{background}$ is the mean pixel value outside the lesion. The maximum diameter of the high and moderate contrast regions were used for comparison with the microscopically measured size of the malignant area in the surgical specimen.

3. RESULTS

In this section we will present one patient measurement from the first phase of the study.

Patient P11-4, a 67 year old Caucasian woman, visited the Center for Breast Care with a palpable lesion in the medial upper quadrant of her right breast. This palpable lesion was highly suspicious upon clinical investigation by a nurse practitioner. The X-ray mammograms of this patient showed relatively dense breast, consisting for about 75% of glandular tissue. The radiologist reported a clear left-right asymmetry and a 2 cm suspicious lesion with a calcification at the position of the palpable mass (Figure 3-left). This lesion was assigned as being a BIRADS V lesion. Ultrasonic evaluation revealed the presence of a hypoechoic lesion with a hyperechoic border. This made the lesion suspicious for being a malignancy. The maximum diameter of this BIRADS IV lesion was 1.75 cm and it was positioned at about 1 cm below the skin (Figure 3-right). The presence of this malignant lesion was confirmed with MRI, which showed a 1.8 cm contrast enhancing mass in the medial part of the right breast.

The patient was measured with PAM before the lesion was biopsied.

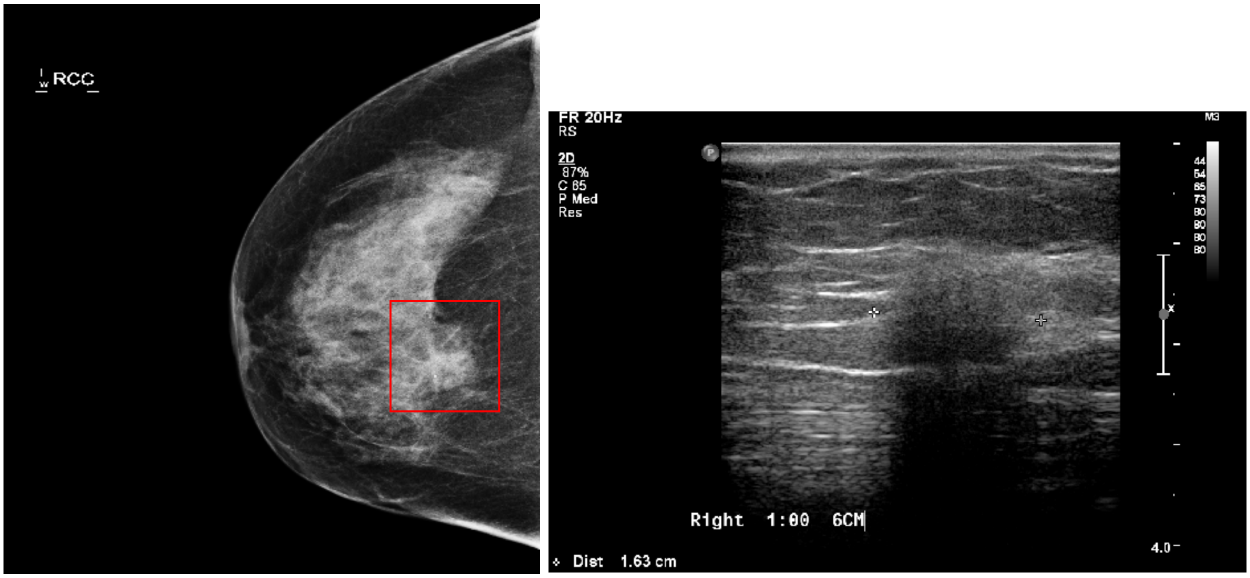

Figure 3: X-ray mammogram (left) and ultrasonography (right) of the patient's suspicious lesion. On x-ray the lesion was assigned as BIRADS V. On ultrasound the lesion was assigned as BIRADS IV.

It was possible to locate the region of interest completely in front of the detector. A beam with a size of 2.8 cm^2 and energy of 57 mJ was used to illuminate the breast. Signals were acquired from 142 elements, corresponding with a scan size of about 41x35 mm^2. The contact with the detector was good and all of the 142 signals could be used for reconstruction. Therefore, this measurement was assigned as being technically acceptable.

A region with high contrast could be seen at a depth between 15 and 19 mm (Figure 4). This region is probably the lesion that can be seen on XRM, US and MRI. Using a threshold of 50% to define this lesion, gave a maximum SNR of 5.9 and a maximum diameter of 10 mm. Lowering the threshold to 25% gave a maximum diameter of 20 mm.

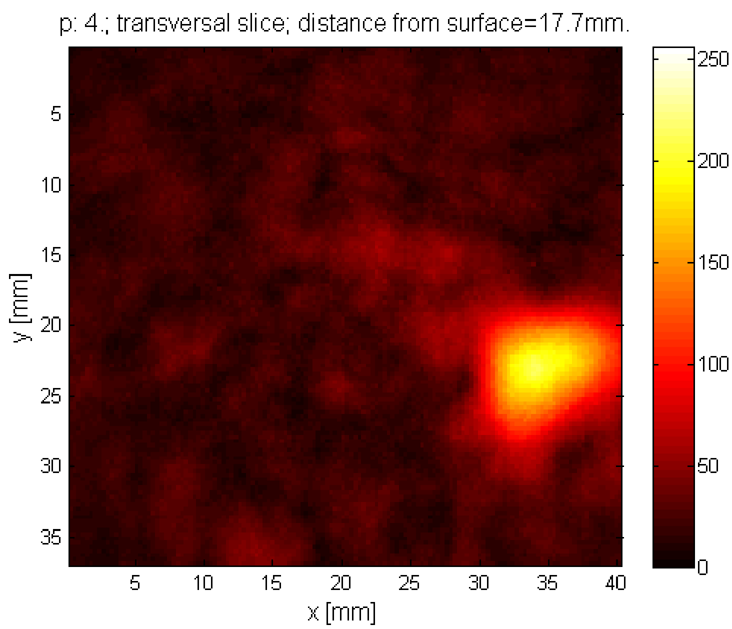

Figure 4: Photoacoustic image of the suggestive lesion. This image shows a transversal slice through the reconstructed volume. The lesion is positioned 15-19 mm below the breast surface and has a maximum SNR of 5.9.

After the photoacoustic measurement, this patient got an ultrasound guided biopsy of the suspicious lesion. Histopathological assessment of the specimen showed signs of an infiltrating ductal carcinoma. Histopathological assessment of the lump after lumpectomy revealed the presence of a 1.5-2 cm large, grade II infiltrating ductal carcinoma without in situ components outside the lesion.

4. DISCUSSION

Recently a new clinical study with the Twente Photoacoustic Mammoscope (PAM) has been started. Based on results from a previous pilot study[12], a study has been designed to find the photoacoustic markers that are indicative for the presence of a malignancy and to guide developments towards future generations of PAM.

The case presented here shows a lesion that is clearly visible on both XRM and US. In addition, the lesion showed a high contrast with respect to the background on the photoacoustic image. This made it suggestive for presenting local high NIR light absorption by hemoglobin as a consequence of tumor angiogenesis. Histopathological assessment proved that this lesion was an infiltrating ductal carcinoma. The depth of the lesion corresponded with the ultrasonographically estimated depth of the lesion. However, the size of the lesion was rather small compared to the histopathologically estimated size. This can be caused by multiple reasons. First, the size on the photoacoustic image was estimated by taking the maximum diameter of the high-contrast region. The high-contrast region was defined as the area in which all pixels had a value of 50% of the maximum pixel value in the specific slice. This 50% is an arbitrary value and it is not known if this threshold gives a good delineation of the malignant area. It was seen that the maximum diameter of the 25% contrast area was much closer to the real tumor size. Therefore, it has to be investigated in more patients which threshold should be used to define the malignant area. Second, PAM visualizes the increased tumor vascularization and it needs to be seen whether the vascularization borders truly match the neoplastic borders. Third, because of the limited scan size only a limited number of signals were used to reconstruct the lesion. This might cause shape and size deviations, which can be overcome by extending the measurement area.

5. CONCLUSION

Photoacoustic imaging might be a useful adjunct to the conventional imaging modalities for breast cancer diagnosis. By using NIR light absorption, some important limitations of x-ray mammography (use of ionizing radiation and influence of breast density) and ultrasound imaging (poor contrast and user dependency) might be overcome. Moreover, the ultrasound detection gives the technique a better resolution and imaging depth than pure optical imaging techniques.

Until now, 12 patients with a breast malignancy have been measured within the new Photoacoustic Mammography study. Here we showed a representative case report of a patient with an infiltrating ductal carcinoma. PAM was able to locate this lesion at a depth of more than 15 mm with a slight underestimation of the malignancy size.

6. CONFLICTS OF INTEREST

W.S., T.v.L. and S.M. have financial interest in PA Imaging Holding BV, which however did not support this work.

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