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Clinical photoacoustic breast imaging: the Twente experience

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Breast cancer is globally the most frequently occurring malignancy in women, and the leading cause of cancer death with up to 0.5 million women dying of the disease in 2008. Early detection and accurate diagnosis of breast cancer is crucial for optimizing survival chances, with imaging technologies playing a major role. X-ray mammography (XRM) and ultrasound (US) imaging, however, suffer from non-optimal sensitivity and specificity. Further, XRM uses ionizing radiation, painful breast compression and has poor performance in dense breasts. For US imaging, inter-operator dependence and poor soft tissue contrast are drawbacks.

Angiogenesis, the production of new blood vessels, has been proposed as an integral hallmark of cancer. This process results in a locally increased abnormal vascularity at tumor sites. Magnetic Resonance Imaging (MRI) exploits the presence of this vasculature for high sensitive imaging of cancer, by visualization of extravasation of contrast agent from the vessels. However, the method suffers from limited specificity and requires contrast agents.

The increased concentrations of hemoglobin (Hb) associated with vascularity, can betray the presence of the carcinoma to light without recourse to contrast agents due to Hb's strong optical absorption. Photoacoustic (PA) also called optoacoustic (OA) imaging uses light as the probe energy, but measures ultrasound (US) instead of photons for the signal. This is because laser-induced US is generated following absorption of short light pulses. The US waves propagate to the surface with low scattering and finite (known) velocity, where they are detected using US detectors, and the origin of the acoustic sources

localized. Thus, while detection of light, would have resulted in washed-out detail due to scattering, detection of US provides high spatial resolution since US is scattered minimally in soft tissue.

Since the application of near-infrared (NIR) PA for breast imaging was first suggested in 1994 [1,2] a few breast imaging prototypes have been showcased and just over 100 patients have been imaged.

Materials and Methods

In 2005, we presented the Twente Photoacoustic Mammoscope (PAM) which uses a 2D US detector matrix. PAM is built into a hospital bed on which the patient lies prone with her breast through an aperture. Under the bed, the breast is slightly compressed between a glass plate for laser illumination, with the US detector array on the opposite side. (**Figure 1**) Pulsed light (10 ns) at 1064 nm is used for illumination, at a radiant exposure of 10 mJ cm^{-2} in the 35 mm^2 beam, ten times lower than the maximum permissible exposure (MPE) on skin. The PA signals are detected using the detector matrix with 588 unfocused elements of size 2x2 mm. The PVDF elements have a central frequency of 1 MHz with a 130% bandwidth. They are distributed in a roughly circular shape with a diameter of 85 mm. US gel is used for acoustic coupling between the breast and detector. Image reconstruction is based on off-line 3D acoustic backprojection.

Testing of patient safety aspects of the instrumentation was conducted prior to each study by the Medical Instrumentation department of the Medisch Spectrum Twente (MST) The study protocols and informed consent procedures were approved by the Medical Ethics Review Board of MST. All patients followed the normal diagnostic pathway. (**Figure 2**) When patients met inclusion criteria for the specific study, breasts were imaged using PAM after conventional imaging, but prior to core needle biopsy to preclude imaging possible internal bleeding following needle insertion. In all cases, breast density was evaluated by 2 (or 3) radiologists reviewing XRMs.

In 2007, we reported the first peer-reviewed results of NIR-PA imaging of breast cancer in patients. [3] In 4 of the 5 malignancies, the PA images with field-of-view of 45x45 mm^2, showed regions of higher intensity, which we attributed to cancer vascularization. Since these successful proof-of-

principle studies, we have performed PAMmography (mammography using PAM) on 51 abnormalities comprising 41 malignancies, 7 cysts, 2 fibroadenoma and 1 chronic active inflammation.

From our experiences we make the following observations and recommendations:

1) PAMmography can visualize infiltrating ductal carcinoma with high contrast

We presented results from an extended clinical study using PAM in 2012 [4] where we investigated the appearance of highly suspicious (BI-RADS 5) breast lesions in 10 patients. The highlights of this work are:

- All 10 malignant lesions [infiltrating ductal carcinomas (IDC)] were visualized in the PA images in the form of a confined region with high contrast,
- The PA contrast of the lesions varied from 3.2 to 7.0 with an average contrast of 5.0.
- In all malignancies, the PA lesion contrast was higher than the contrast in XRM.

In latest work [5] we describe results obtained on imaging 31 malignancies (predominantly IDC) using PAM, with a FOV of 85x85 mm. In 30 cases the lesion was identified unambiguously with PA contrasts ranging from 2.2 to 7.0 with an average contrast of 3.6. This shows compelling evidence that PA imaging has potential for visualizing breast cancer with high contrast.

2) PA lesion contrast is not dependent on radiographic breast density

The average PA and XRM lesion contrasts were compared against breast density in the 2012 study on 10 lesions. Based on assessment by 2 radiologists using BI-RADS density criteria, a two-scale classification was used (low: BI-RADS density 1, 2 and high: BI-RADS density 3, 4). In the latest study [5] the same analyses were performed on 31 lesions**.** The findings in the two studies are that there are no significant differences in average PA contrast between the high and low density groups. Lower x-ray lesion contrasts were recorded in high density breasts, and 1 lesion was missed in the 2007 study and 3 missed in the 2012 study.

This early finding is very promising for the use of PAMmography in breasts rich in radiodense glandular tissue as in pre-menopausal subjects, where XRM is known to show reduced accuracy with sensitivity falling from around 90% to 40-60%.

3) Breast malignancies show signature PA presentations

We studied the PA appearances of IDC [6] and whether these could be related to tumor vasculature. In addition to comparisons with XRM and US imaging, PA images were compared with MR images and with vascular staining in histopathology. Lesions were found to present with various appearances similar to contrast enhancement types reported in MRI of breast malignancies. The following PA image patterns were found: 1) Mass appearance; 2) Ring appearance; and 3) Non-mass appearance. MR images were available for a total of 11 cases, and correspondence was very good to excellent. (**Figure 3**) In 6 cases, CD-31 immunohistochemistry (IHC) on tissue sections, showed good correspondence between density and distribution of vascularity and PA image patterns. (**Figure 3**) These findings are significant as they can contribute to the development of PA image descriptors as diagnostic criteria in the future.

4) Breast cysts show specific PA appearances

The PA visibility of benign breast cysts using 1064 nm light was investigated.[7] It was found that depending on the absorption contrast between cyst and breast tissue, cysts were visible as either one or two confined high contrast areas representing the front, and the front-and-back of the cyst respectively. These features are the consequence of the abrupt change in absorbed energy density and Grüneisen coefficients going across the interfaces, in combination with the limited-view geometry. Cysts can thus be mistaken for malignancies which can also appear as one or multiple confined contrast areas.

Measuring with multiple wavelengths will be required to differentiate Hb absorption associated with malignancies, from the absorption by chromophores more characteristic for cyst fluid.

4) Recommendations and outlook

On the ***Technical side*** the following points require attention in the near-future:

i) **Multispectral excitation**: This will be of utmost importance to discriminate between malignancies and benign abnormalities based on differences in Hb absorption associated with the two types of lesions.

ii) **Quantitation of optical absorption**: The PA images are developed by solving the acoustic inversion problem to recover the initial pressure distribution. The images represent absorbed energy maps - the product of fluence and absorption coefficient. The recovery of absorption coefficient, would permit the estimation of Hb (or other biochrome) concentrations permitting molecular imaging, and in combination with i) lead to estimation of functional measures such oxygen saturation. Quantitative information is expected to provide an additional criterion to discriminate between benign, pre-invasive and malignant lesions. Quantitation, which involves solving the optical inverse problem is nontrivial, but is essential for accurate functional and molecular imaging.

iii) **Tomographic geometry**: A closed detection aperture with reconstructions from multiple projections as in a tomographic imaging geometry will minimize acoustic shadowing effects and provide high resolution approaching the axial resolution of the US detectors.

iv) **Sensitive ultrasound transducers**: High detector sensitivity is required to detect small optical absorption contrasts associated with smaller tumors, or those with lower vascularities. Additionally for faithful registration of objects with various dimensions, the bandwidth (BW) of the detector requires to be broad. This has consequences for sensitivity: increasing BW comes at the cost of sensitivity and *vice versa*. Specialized US transducers are required, developed specifically for the challenging requirements in PA breast imaging.

v) **Multimodal Imaging**: Since the US detection hardware required for both techniques can be shared, PA imaging can be combined with US imaging. A dual mode system with superposition of US images on PA images will give anatomic and structural context to functional detail. Additional parameters estimated from US imaging such as speed of sound and acoustic attenuation can assist in better differentiation

between certain benign lesions such as cysts from tumors, but also assist in enabling quantitative PA imaging.

On the ***clinical side*** we believe the following to be urgent questions in PA breast imaging:

i) What are the PA appearances of infiltrating ductal carcinomas (IDC)? What are the PA features of other lesions such as infiltrating lobular carcinoma (ILC), ductal carcinoma *in situ* (DCIS) and fibroadenomas?

ii) What the pathophysiological reasons for these features? Can these features be related to angiogenic or vascular distributions in pathology? Can these appearances develop into diagnostic indicators for breast cancer?

iii) What are PA image descriptors of the contralateral breast and the healthy breast? Would it be possible to develop criteria for detection?

And finally: iv) What role will photoacoustics play in breast imaging? Is there benefit in diagnosis, detection (screening) or both? Is there benefit in niche areas of neoadjuvant chemotherapy monitoring and imaging of dense breasts?

Concluding remarks

It is clear that instrumentation for PA breast imaging is not yet as sophisticated as required. Further, there are still many lacunae in our understanding of the *in vivo* performance of the method, since the early patient studies have naturally been conservative. However the knowledge gained in the last decade in imaging patients has shown that the method has tremendous potential to impact the clinical breast cancer care model. It is a good time to be in the field of photoacoustic breast imaging.

It should be emphasized, that the path from knowledge which will gained in the future, to accepted clinical practice is long, difficult and expensive. In addition to development of sophisticated instrumentation and early clinical assessment in the academia-hospital nexus, the roles of industry in engineering and development will be important. Further, when knowledge of clinical efficacy becomes clearer in the future, other stakeholders such as organizations that make decisions regarding approval for medical devices, insurance coverages and reimbursements, will become increasingly important.

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COMPETING FINANCIAL INTERESTS

W. S. and S. M. have financial interest in PA Imaging Holding BV., which did not support the work.

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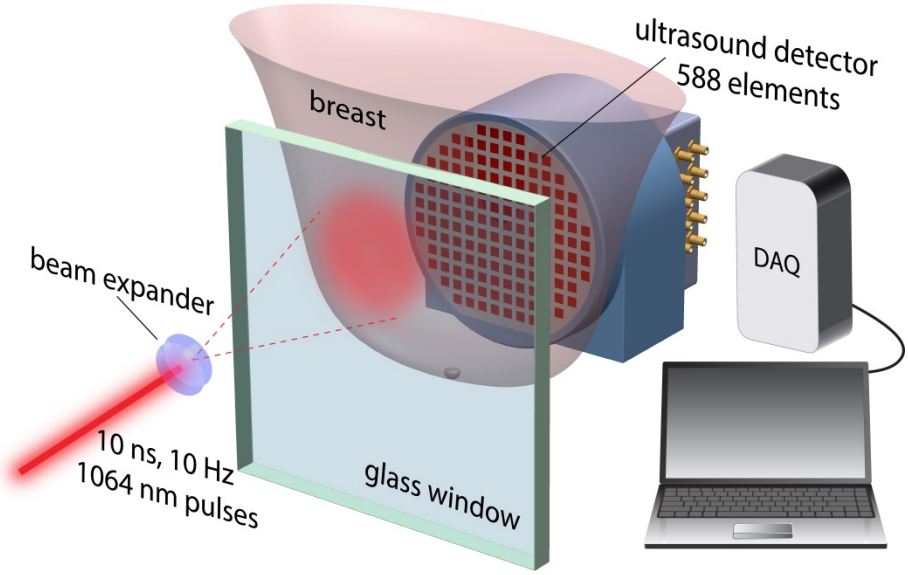

Figure 1: Schematic of the imager of the Twente Photoacoustic Mammoscope: The breast is immobilized between a glass window and an ultrasound detector matrix. Light at 1064 nm from a Q-switched Nd-YAG laser expanded to a diameter of 70 mm illuminates the breast through the window. The 588 detector elements are arranged in a diameter of roughly 85 mm. Analog front-end electronics are mounted close to the detection elements, and the data is digitized and read into the computer for off-line image reconstruction.

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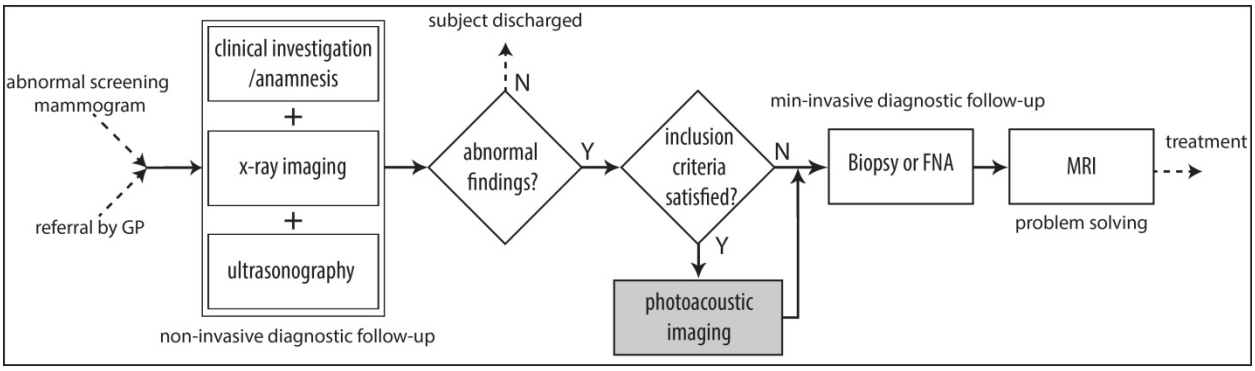

Figure 2: Simplified clinical workflow at the Medisch Spectrum Twente hospital. (Abbreviations: GP – general practioner; FNA – fine needle aspiration; MRI – Magnetic Resonance Imaging.)

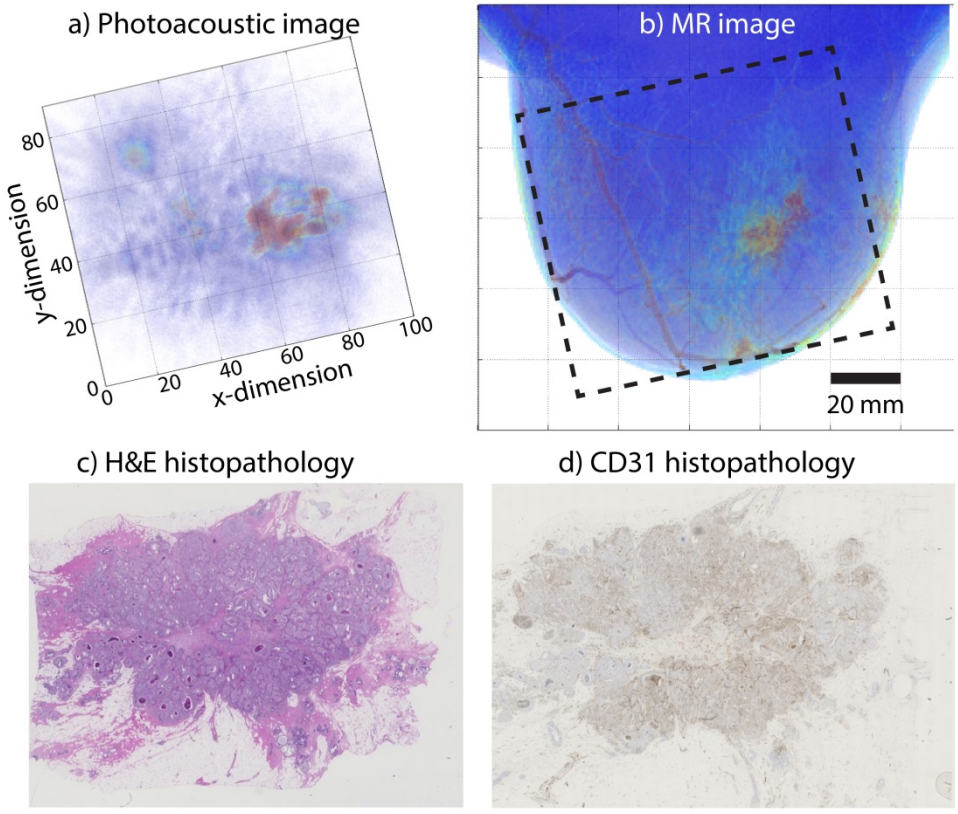

Figure 3: Example of photoacoustic mass appearance seen in 63 year old patient (P55,) with infiltrating ductal carcinoma (IDC). The lesion was highly suspicious on x-ray mammography – XRM (not shown) by the presence of an irregularly shaped, unsharply delineated 20 mm mass. **(a)** The average intensity projection (AIP) PA image, is shown tilted due to the breast being tilted during the PA measurement to position the lesion favorably in front of the detector. In the PA image, the lesion is clearly visible as an irregular, high contrast, 29 mm mass. The lesion co-localized perfectly with the lesion on XRM.(not shown) The lesion also co-localized well with **(b)** the AIP Magnetic Resonance (MR) image after tilting the PA image. The dashed box in the MR image indicates the area from which the PA image is acquired. The MR appearance is described as an irregularly shaped mass **(c)** Histopathological assessment of the tissue specimen post-surgery revealed the presence of a 34 mm IDC, grade 2. **(d)** The CD31 stained tumor slide shows the microvascularity spread over the entire lesion supporting the mass-appearance observed in PA and MR images. It is intriguing that the patterns in (a) – (d) appear roughly similar in appearance.