Photoacoustics 12 (2018) 30–45

Contents lists available at ScienceDirect

Photoacoustics

journal homepage: www.elsevier.com/locate/pacs

Research article

Clinical optoacoustic imaging combined with ultrasound for coregistered functional and anatomical mapping of breast tumors

A.A. Oraevsky[a,*], B. Clingman[b], J. Zalev[c], A.T. Stavros[b], W.T. Yang[d], J.R. Parikh[d]

[a] TomoWave Laboratories, Houston, TX, United States
[b] Seno Medical Instruments, San Antonio, TX, United States
[c] Department of Physics, Ryerson University, Toronto, Canada
[d] Department of Radiology, University of Texas MD Anderson Cancer Center, Houston, TX, United States

ARTICLE INFO

Keywords:
Optoacoustic
Photoacoustic
Ultrasound
Functional-anatomical imaging
Breast cancer
Diagnostics
Dual modality

ABSTRACT

Optoacoustic imaging, based on the differences in optical contrast of blood hemoglobin and oxyhemoglobin, is uniquely suited for the detection of breast vasculature and tumor microvasculature with the inherent capability to differentiate hypoxic from the normally oxygenated tissue. We describe technological details of the clinical ultrasound (US) system with optoacoustic (OA) imaging capabilities developed specifically for diagnostic imaging of breast cancer. The combined OA/US system provides co-registered and fused images of breast morphology based upon gray scale US with the functional parameters of total hemoglobin and blood oxygen saturation in the tumor angiogenesis related microvasculature based upon OA images. The system component that enabled clinical utility of functional OA imaging is the hand-held probe that utilizes a linear array of ultrasonic transducers sensitive within an ultrawide-band of acoustic frequencies from 0.1 MHz to 12 MHz when loaded to the high-impedance input of the low-noise analog preamplifier. The fiberoptic light delivery system integrated into a dual modality probe through a patented design allowed acquisition of OA images while minimizing typical artefacts associated with pulsed laser illumination of skin and the probe components in the US detection path. We report technical advances of the OA/US imaging system that enabled its demonstrated clinical viability. The prototype system performance was validated in well-defined tissue phantoms. Then a commercial prototype system named Imagio™ was produced and tested in a multicenter clinical trial termed PIONEER. We present examples of clinical images which demonstrate that the spatio-temporal co-registration of functional and anatomical images permit radiological assessment of the vascular pattern around tumors, microvascular density of tumors as well as the relative values of the total hemoglobin [tHb] and blood oxygen saturation [sO2] in tumors relative to adjacent normal breast tissues. The co-registration technology enables increased accuracy of radiologist assessment of malignancy by confirming, upgrading and/or downgrading US categorization of breast tumors according to Breast Imaging Reporting And Data System (BI-RADS). Microscopic histologic examinations on the biopsied tissue of the imaged tumors served as a gold standard in verifying the functional and anatomic interpretations of the OA/US image feature analysis.

1. Introduction

Breast cancer is the most common type of cancer in women and the second leading cause of death due to cancer among women in the United States. The American Cancer Society (ACS) estimates that 40,290 women will die from breast cancer in the United States [1,2]. Mammography is the most common imaging modality currently used for population screening and the early detection of breast cancer. While the sensitivity of screening mammography is about 87.0% in women with almost entirely fatty breasts, higher breast density and heterogeneity of breast parenchymal density limits the sensitivity of mammography to about 29–63% [2,3]. The average positive predictive value (PPV1) of mammography is only 50–60% [4]. In balancing the detection error rates against the potential harm of cumulative ionizing radiation, the ACS guidelines no longer recommend routine screening (x-ray) mammograms for patients younger than 45 years old with an average risk of breast cancer [2]. The ACS guidelines do still recommend bi-annual screening mammograms for women beyond 45 years old [2].

Diagnostic US is widely performed in the workup of abnormal

* Corresponding author.
E-mail address: aao@tomowave.com (A.A. Oraevsky).

https://doi.org/10.1016/j.pacs.2018.08.003
Received 13 May 2018; Received in revised form 31 July 2018; Accepted 22 August 2018
Available online 31 August 2018

mammography findings. Advantages of US include its safety, convenience and capability to visualize tumors with video rate display that are radiologically occult, lack of ionizing radiation, and relatively low cost. Targeted diagnostic breast ultrasound helps in classifying breast cancer with excellent sensitivity, but suffers from low specificity. Ultrasound diagnosis of breast cancer has been primarily based on the lesion morphology (shape characteristics and ultrasound properties). Many malignant breast masses are too small to present sufficiently distinctive features on conventional ultrasound. Thus, the positive predictive value of the diagnostic ultrasound imaging after mammography and diagnostic ultrasound in biopsied masses (PPV3) is under 30% [5]. When the ultrasound results are abnormal or indeterminate, the radiologist typically recommends that a biopsy is performed of the lesion. Because of the low PPV3, over 70% of breast biopsies are performed on benign lesions. This high false positive biopsy rate leads to about 1.6 Million unnecessary biopsy procedures with associated medical expenses of over $3Billion, patient and family anxiety, and patient discomfort from the procedure [6]. The false positive rate of supplemental screening breast ultrasound has been even higher than that of diagnostic breast ultrasound (as low as 8% PPV3 in the ACRIN 6666 trial), and has been a major obstacle to the adoption of supplemental breast ultrasound screening in women with radiologically dense and heterogeneous breast tissue [7].

1.1. Background and significance

We present a newly developed technology of combined optoacoustic plus ultrasound (OA/US) imaging, integrated in the Imagio™ breast imaging system, specifically designed for imaging of breast and diagnosis of breast masses. This technology provides a two-fold enhancement of the overall diagnostic accuracy, combining specificity from functional imaging with molecular specificity of hemoglobin and oxyhemoglobin with the 95-plus% sensitivity of breast ultrasound anatomical imaging [8]. We describe the OA/US system technical parameters and the design methods that enabled these advanced specifications. The design of laser, fiberoptic components, and an OA/US handheld probe enable generation of OA images while retaining all the advantages of breast ultrasound, including interactive real-time imaging, providing high contrast, high resolution images with visualization of breast and tumor morphology. We also discuss our signal processing, image reconstruction and post-processing to achieve precise co-registration and overlay of OA images with conventional ultrasound images to visualize hemoglobin distribution and blood oxygen saturation in the context of breast morphology. The system was validated in well-characterized breast tissue mimicking phantoms. Finally, we present examples of clinical images that demonstrate the clinical value of Imagio™ as a diagnostic imaging modality, with the potential to decrease false-positive mammography findings.

1.2. Fundamentals of optoacoustic imaging

For clinical radiologists, “seeing is believing”. Therefore, optical imaging technologies are naturally suited for medical applications. However, due to optical scattering, pure optical modalities that illuminate and sense light are not able to achieve adequate depth penetration and spatial resolution in the thickness of breast tissue necessary for complete evaluation of normal breast tissue [9]. Optoacoustic (photoacoustic) imaging was proposed to alleviate the problem of strong optical scattering within tissues [10,11]. This fusion of optical imaging and acoustic imaging uses the most compelling properties of light (high and spectrally selective optical contrast of molecules) and sound (high spatial and temporal resolution enabled by ultrasound propagating in tissues with relatively low attenuation to greater depths than can be achieved by optical imaging alone). Optoacoustic imaging is a method of deeper tissue visualization based on time-resolved detection of acoustic pressure profiles induced in tissue through absorption of near-infrared laser pulses with the pulse duration shorter than the time it takes for the optically generated ultrasound to propagate with the speed of sound through a voxel of tissue to be resolved on the image [12]. Out of numerous molecules that compose human tissue, five chromophores: hemoglobin, oxyhemoglobin, lipids, melanin and water considerably absorb deeply penetrating near-infrared (NIR) light [13]. The absorbed optical energy is converted into heat, causing a transient thermoelastic expansion that generates OA waves from the voxels that absorb NIR light stronger than the background tissue. These OA waves can be detected by an array of ultrasonic transducers and the detected and digitized signals can be used to reconstruct images using tomography algorithms [14]. If the laser wavelength matches (or close to) the peak optical absorption of one of the five dominant NIR chromophores, then the corresponding OA image can visualize tissues abundant with that specific molecule: hemoglobin in veins, oxyhemoglobin in arteries, lipids in nerves, melanin in skin and water in aqueous tissues. Since blood is the most important in supporting normal functioning of live tissues with oxygen and energy, OA images of blood distribution and its oxygen saturation have the highest medical relevance. OA imaging of the total hemoglobin [tHb] and blood oxygen saturation [sO2] represents functional imaging technology rather than tissue morphology. Due to relatively smooth distribution of diffuse blood in tissues, OA images lack vivid anatomical context with the exception of circulation (vasculature and microvasculature).

1.3. Dual modality systems

In the early years of development, OA imaging researchers realized that B-mode gray scale ultrasound imaging based on contrast provided by the acoustic impedance is complementary to the nature of medical information provided by the functional optoacoustic images [15,16]. The dual modality has the merit of images based on two different contrast mechanisms, functional optical and anatomical ultrasound, to be co-registered and temporally interleaved in real time, which in turn enhances each technology and can achieve greater clinical performance.

Furthermore, combining the two systems in one modality is acceptable to radiologists because they can readily adapt and associate functional information with morphology provided by co-registration of the optoacoustic and ultrasound images. With this understanding, a number of groups developed optoacoustic ultrasonic dual modality systems based on commercial ultrasound machines and commercial pulsed lasers (see, for example [17–21]). While these dual modalities take some advantage of the optical contrast in live tissues in addition to the acoustic impedance contrast of ultrasound imaging, all such system have one significant limitation. Medical ultrasound machines use relatively narrow band ultrasound transducers (central frequency ± 40%) that emit reverberating train of ~3 ultrasonic pulses. These pulses are enveloped upon detection using Hilbert transform and can be used to reconstruct high-resolution images with maximum emitted frequency of 10–15 MHz. The need for such high frequencies limits penetration depth of medical ultrasound. However, the penetration depth of about 40–50 mm is sufficient for many medical imaging applications, including diagnostic imaging of breast cancer. On the other hand, the merit of optoacoustic imaging is to provide quantitative functional and molecular information from the volume of tissue structures. This type of information cannot be attained from the boundaries of blood vessels, tumors and other physiologically important tissue structures. Therefore, optoacoustic imaging requires that ultrasound detectors maintain sufficient sensitivity in the range of the lower frequencies down to 50–100 kHz. We termed this type of detectors “ultrawide-band ultrasonic transducers” [12]. Below, we describe the advanced features in the design of the optoacoustic plus ultrasound hand-held dual modality probe, the corresponding electronics hardware, and system software, which resolve prior technological challenges and enable viable clinical performance of Imagio™ for purposes of more accurate diagnosis of breast cancer.