Photoacoustic dual-scan mammoscope: results from 38 patients

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Abstract: We have developed a photoacoustics-based imaging system, the dual-scan mammoscope (DSM), that combines optical contrasts with acoustic detection, to obtain the angiographic features in human breast. In this study, we investigated whether the system can differentiate malignant tumor and healthy breast. We have imaged 38 patients with various tumor types and compared results of tumor-bearing breast with healthy breast for each patient. We also compared the photoacoustic and ultrasound imaging results with clinical US. Vascular features in and around the tumor mass were visualized. We found that tumor-bearing breast contained vessels of larger caliber and exhibited stronger variations in the background signals than those in the contralateral healthy breasts. Preliminary data on photoacoustic and ultrasound images also indicate that the technique has potential in differentiating different tumor types. Overall, our results indicate that combining photoacoustic and ultrasound images can improve breast cancer screening.

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1. Introduction

Breast cancer is the most common forms of cancer among women worldwide, where more than 40,000 patients succumb to in the United States [1]. Early detection is one of the key factors to improve survival [2]. Existing imaging techniques like mammography or ultrasound (US) often rely on morphological changes to detect tumor from healthy tissue. However, many times tumors are either falsely detected or completely missed [3]. Mammography is the most accepted and widely used screening modality; however, it has decreased sensitivity to breast cancer in dense breast tissue despite the fact that those women are at a higher risk for breast cancer [4]. Mammography requires compression of the breasts between metal plates that cause a lot of discomfort to the patients, particularly when the breast size is smaller. Also, it exposes the patient to ionizing radiation [5]. While ultrasound is patient-friendly and has better sensitivity than mammography for dense breasts, it is prone to false positives and is heavily operator dependent [6]. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has good sensitivity and specificity for dense breasts. However, it is an expensive procedure and also requires an injection of Gadolinium as a contrast agent. In certain cases, this can lead to an allergic reaction, renal failure, or deposition in the central nervous system [7–9]. Therefore, there is a need for new imaging modalities with better sensitivity towards dense breast tissue.

Photoacoustics (PA) is a hybrid imaging modality that uses laser light as an excitation source on biological tissue. When pulsed laser light is incident on a biological tissue sample, it leads to thermoelastic expansion, which induces pressure waves. The pressure waves can be detected using an acoustic detector. Thus, PA combines optical contrast with ultrasound detection, which achieves better penetration depth when compared to purely optical imaging techniques [10].
As breast tumors develop, functional changes occur well before morphological changes occur [11]. For instance, in rapidly growing tumors more than 2 mm in diameter, angiogenesis and increased micro-vessel density are evident as the higher tumor growth requires oxygen and nourishment. Therefore, the elevated hemoglobin (which delivers oxygen) level in the suspicious region is an indicator of cancer [12]. Since hemoglobin is the main absorber in the near-infrared region (NIR), blood can act as endogenous contrast in PA imaging [13]. Therefore, NIR wavelengths, such as 800 nm and 1064 nm, are used in PA imaging to visualize the angiographic features [14].

In our previous work, we have discussed the development of Dual-scan Mammoscope (DSM) and its initial imaging results [15]. In this paper, we discuss DSM results obtained from 38 patients. The goal of this study is to identify PA features of breast cancer and investigate future direction for system development.

2. Methods

2.1. Imaging protocol

The study protocol was approved by the institution review board of University at Buffalo and Roswell Park Comprehensive Cancer Center. Patients with biopsy-proven breast cancer were included in the study. Roswell Park patients were recruited by a study nurse and breast surgeons, while Windsong patients were recruited by patient navigators. Pregnant women and women with implants were excluded. Written consent was obtained after ensuring the patients had understood the implication of participation. Diagnostic X-ray mammogram, ultrasound imaging and contrast MRI results were obtained from the imaging clinic along with pathology reports. The tumor location, size, and type were ascertained before the imaging procedure. For this study, we mainly focused on malignant cases.

2.2. Imaging procedure

The DSM consists of an upright geometry where the breast is placed between two water tanks and mildly compressed using plastic films in the craniocaudal plane. Both water tanks are filled with deionized water (DI water) to minimize air bubbles. The bottom water tank is fixed on an optical breadboard and the lift-table is adjusted such that the patient can stand comfortably. Figure 1 gives a schematic of the DSM set-up. The details are discussed in our previous work [15]. We first put ultrasound gel on the plastic film of the bottom tank and placed the breast on it. Then, we applied ultrasound gel to the top surface of the breast and gradually rolled down the top water tank until the desired breast compression is achieved. The scan-head in each water tank consists of a line output fiber bundle and a 2.25MHz linear array transducer positioned in a double reflector setup as shown in Fig. 1. After making sure that both transducers are positioned correctly, the breast is scanned along its length with a step size of 0.1 mm/laser pulse. We determine the scanning time based on the length of breast tissue that has been compressed craniocaudally. For example, the scan time for a 6 cm breast is 60 seconds with a step size of 0.1 mm/pulse. A 256-channel data acquisition system (Verasonics, Inc.) is used to acquire both US and PA data simultaneously in an interleaved fashion. US images for DSM are acquired through spatial compounding with 5 acquisition angles for improved US contrast. After imaging the first breast, we clean the plastic films with disinfection wipes to remove excess gel and image the other breast in a similar fashion. There is no need to replace water as it does not come in contact with the patient. Therefore, the imaging procedure is very fast. The actual scanning time for one breast is 1 minute and the complete imaging session, including patient preparation, took about 15 minutes. As the compression was achieved through plastic membranes and much milder than X-ray mammography, patients did not feel any pain during the imaging procedure.
2.3. Reconstruction and data analysis

The Verasonics system’s built-in algorithm was used for US reconstruction. The PA raw-channel data was first weighted over depth to compensate for the exponential loss in optical signal and then reconstructed using the universal back-projection algorithm [16]. The compensation function for the left and right breasts of the same patient was the same. Therefore, the weighting does not affect the statistical analysis. The weighting factors could be different among patients, as different patients might have different tissue structures and densities. Based on the scanning position, the reconstructed cross-sectional images were stacked to form a 3D matrix. In order to analyze the PA features, image segmentation was performed on the reconstructed and normalized PA data. To segment vessels and background, we first apply vessel enhancement through Frangi filtering [17] and the resulting image was used to create a mask for future analysis. The average vessel signal (vessel mean) and standard deviation, along with background standard deviation, were calculated from this mask. For statistical analysis, the PA features analyzed for each data set were the vessel contrast, average vessel signal, and standard deviation of vessel and background (Table 1). Each parameter was quantified as the ratio of values in tumor-bearing breast and health breast of the same patient. For instance, the vessel signal ratio is the ratio of average vessel signal for tumor-bearing to healthy breasts. As shown in Table 1, we chose these parameters for our analysis as they provide an insight into PA signal changes and its significance for tumor vs healthy tissues.

| Parameter               | Calculation                                                                 | Significance                                                                 |
|-------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Vessel mean ratio       | \[ \text{Vessel mean ratio} = \frac{\text{tumor(vessel mean)}}{\text{healthy(vessel mean)}} \] | This parameter is related to the vessel diameter and blood volume.            |
| Contrast ratio          | \[ \text{Contrast ratio} = \frac{\text{tumor(vessel/background)}}{\text{healthy(vessel/background)}} \] | This parameter indicates the strength of vessel signals in comparison to the background (tissue, microvasculature). |
| Standard deviation ratio (vessel) | \[ \text{Std.dev vessel} = \frac{\text{std.dev (vessel)}}{\text{std.dev (vessel)}} \] | This parameter is related to the variations in vessel diameter and volume.    |
| Standard deviation ratio (background) | \[ \text{Std.dev background} = \frac{\text{std.dev (background)}}{\text{std.dev (background)}} \] | This parameter is related to the variations in background signal (tissue, microvasculature). |
3. Results

In this study, 38 patients with biopsy-proven malignancies in one breast were imaged using the DSM. Among these, 28 were cases of infiltrating ductal carcinoma (IDC), 6 were ductal carcinoma in situ (DCIS) and 5 of invasive lobular carcinoma (ILC). Of the 28 IDC cases, 20 were cases of IDC only and 8 were IDC and DCIS combined. The average age was 54 years (36 to 77 years), and the tumor size ranges from 0.04 to 4.90 cm², as shown in Table 2. The tumors were relatively evenly distributed within this size range, with \(\sim 68\%\) tumors less than 2 cm².

### Table 2. Summary of patient data

| Patient Data                  | No. of patients |
|-----------------------------|-----------------|
| Total number of patients    | 38              |
| Breast Density              |                 |
| Scattered fibroglandular density (23) |               |
| Heterogeneously Dense (11) |                 |
| Extremely Dense (4)         |                 |
| Tumor size range            | 0.04–4.9 sq. cm |
| Tumor type                  |                 |
| IDC (28)                    |                 |
| DCIS (5)                    |                 |
| ILC (5)                     |                 |

3.1. Statistical analysis

Statistical analysis was performed using MATLAB. All hypothesis tests used a type I error rate of 0.05 (\(\alpha\)). In this study, we used upper-tailed t-tests to compare different parameters for tumor and healthy breasts. Each null hypothesis assumed that there is no difference between the tumor-bearing and healthy breasts.

Table 3 summarizes our statistical results. Four top data were excluded due to poor data quality caused by inadequate coupling with the plastic membrane. When all cases were taken together, we found that the tumor-bearing breast exhibited stronger vessel signal intensity in comparison to the healthy breast (Top data: \(P = 0.020\); Bottom data: \(P = 0.055\)). This observation indicates the presence of larger vessels in tumor-bearing breast which can be seen clearly in Fig. 2. Our finding aligns with the published study that states malignant tumors exhibit an increase in vascular caliber and regional vascularity [18]. There is also a strong statistical significance that tumor breasts exhibit higher contrast ratio (Top data: \(P = 0.0029\); Bottom data: \(P = 0.057\)). This result is consistent with our findings on the vessel mean ratio, as stronger vessel signals will result in a higher vessel contrast. The standard deviation in background signal (Top data: \(P = 0.030\); Bottom data: \(P = 0.035\)) is also found to be higher in tumor breasts, indicating strong variation in tissue signals, possibly caused by growing of microvasculature. On the other hand, the ratio of standard deviation of vessel signals in tumor-healthy breasts (Top data: \(P = 0.069\); Bottom data: \(P = 0.067\)) is not as significant as that of background. Overall, these observations are consistent

### Table 3. Statistical test results.

| Data                                                   | Vessel Mean | Contrast Ratio | Standard Deviation (Background) | Standard Deviation (Vessel) |
|--------------------------------------------------------|-------------|----------------|---------------------------------|----------------------------|
| Images acquired by bottom transducer (38) [h, p]      | [0, 0.055]  | [0, 0.057]     | [1, 0.035]                      | [0, 0.067]                 |
| Images acquired by top transducer (34) [h, p]        | [1, 0.020]  | [1, 0.0029]    | [1, 0.030]                      | [0, 0.069]                 |

\(^a\)h = 1 indicates that the test rejects the null hypothesis and the PA feature in tumor-bearing breast is stronger.
with published photoacoustic and breast imaging studies indicating higher blood volume and vascular activities in the tumor-bearing breast [14,19,20]. However, this is the first investigation that reported a difference in the vessel signal intensity/diameter and background variation.

**Fig. 2.** Maximum amplitude project (MAP) images of PA results for statistical analysis plotted in craniocaudal (CC) view. (a, c) Tumor-bearing breasts, (b, d) healthy breasts. Data from the same patient (images in the same row) was plotted using the same color scale. PA vascular features in tumor-bearing breast exhibit stronger signal intensity.

In general, images acquired by the top transducer perform better in the statistical analysis because a majority (~80%) of imaged tumors are in the top portion of the breast. In order to validate this, we also performed an upper tailed t-test on only the top data. We found that our P-values have greater significance when the test was performed this way (Table 4).

**Table 4.** Statistical results with only top tumor data.

| Data                  | Vessel Mean | Contrast Ratio | Standard Deviation (B) | Standard Deviation (V) |
|-----------------------|-------------|----------------|------------------------|------------------------|
| Top data (25) [h, p]  | [1, 0.016]  | [1, 0.0068]    | [1, 0.050]             | [1, 0.014]             |

### 3.2. Preliminary findings on tumor subtypes

In this section, we show the morphological and vascular tumor features as captured by the DSM. These preliminary findings are to show different tumor subtypes in PA when compared to clinical US results.

The first exemplary result is acquired from a 50-year-old patient diagnosed with invasive ductal carcinoma, SBR grade II, with biopsy results indicating tumor subtype of luminal A [ER+, PR+, HER2-] (LUMA). The tumor mass indicated is identified with the aid of US data acquired by the DSM. In comparison to clinical US [Fig. 3(a)], the DSM images in Fig. 3(b) showed similar tumor morphology. We observed that there are more vascular features at the periphery of the tumor in comparison to internal vessels [Fig. 3(b)]. This result is consistent with the published PA literature on tumor subtype of LUMA [20–23].
**Fig. 3.** 50-year-old patient with invasive ductal carcinoma, SBR grade II with scattered fibroglandular breast density. The tumor mass is marked with an asterisk in all figures. (a) Clinical ultrasound image shows the tumor mass. (b) Grayscale US acquired from DSM. PA features are shown in color scale as they represent the hemoglobin map in the breast: stronger PA amplitudes indicate a higher concentration of hemoglobin. The PA features can be added to the morphological features from US. Most PA features are concentrated at the periphery of the tumor. The ultrasound image in (a) was sized to share the same scale bar in (b).

The second exemplary result is acquired from a 49-year-old patient with scattered fibroglandular breast density. This patient is diagnosed with infiltrating ductal carcinoma, architecturally poorly

**Fig. 4.** 49-year-old patient with infiltrating ductal carcinoma, with scattered fibroglandular breast density. The tumor is marked with an asterisk in all figures. (a) Clinical ultrasound image shows the tumor mass. (b) Grayscale US acquired from DSM. PA features (color scale) represent the hemoglobin map in the breast, which can be added to the morphological features from US. Most PA features are present inside the tumor region. The ultrasound image in (a) was sized to share the same scale bar in (b).
differentiated, high nuclear grade, and SBR grade III. The biopsy results indicating a tumor subtype of triple-negative breast cancer [ER-, PR-, HER2-] (TNBC). The clinical US image is shown in Fig. 4(a), while the DSM images (color-scale PA image overlaid on the grayscale US) are shown in Fig. 4(b). The tumor mass is marked with an asterisk. We observed that the PA features [Fig. 4(b)] reveal more internal vascular features than in surrounding tissue. This result is consistent with published literature for the TNBC subtype\textsuperscript{20–23}.

The third exemplary result is acquired from a 62-year-old patient, with scattered fibroglandular breast density, diagnosed with infiltrating ductal carcinoma, histologic grade 2, nuclear grade 2. The biopsy results indicating tumor subtype of luminal B (ER+, PR+, HER2-) [LUMB]. The clinical US image is shown in Fig. 5(a), while Fig. 5(b) shows PA (color scale) and US (grayscale) results from DSM systems overlaid. In this case, the tumor mass was identified based on structures indicated with white arrows in the clinical US and DSM image. We observed that the tumor mass showed an increased PA signal intensity in comparison to surrounding healthy tissue [Fig. 5(b)]. This is also consistent with published literature for LUMB cancer subtype\textsuperscript{20–23}.

![Fig. 5. 62-year-old patient with infiltrating ductal carcinoma, with scattered fibroglandular breast density. The tumor is marked with an asterisk in all figures. (a) Clinical ultrasound image shows the tumor mass. (b) Grayscale US acquired from DSM. PA features (color scale) represent the hemoglobin map in the breast, which can be added to the morphological features from US. PA features can be found in and around the tumor region. The tumor is identified based on the morphological features indicated by white arrows. The ultrasound image in (a) was sized to share the same scale bar in (b).](image)

4. Discussion

The results from our statistical analysis indicate that the tumor-bearing breast exhibits stronger vessel signal and vessel contrast, as well as larger variations in background signal. These results imply larger vessels and increased microvasculature in the tumor-bearing breast. Overall, these conclusions are consistent with published results that indicate tumor angiogenesis as a biomarker for malignancy \textsuperscript{24}. Furthermore, we hypothesize that different tumor types exhibit different PA features because of differences in proliferation rates, histological structures, metastatic patterns, etc \textsuperscript{25,26}. For instance, published studies showed that ILC had a slower proliferation rate and lower expression of vascular endothelial growth factor (VEGF) in comparison to IDC \textsuperscript{27–30}. 
As VEGF is the mediator of pathological angiogenesis [31], it is possible that there may be a difference in PA features for IDC and ILC cases. We have conducted the same statistical analysis for each tumor type. We found that the contrast ratio and standard deviation of vessel ratio are stronger in IDC-bearing breasts than in contralateral healthy ones. Other breast tumor types, due to the small case number (Table 2), did not reveal statistically significant results. Further study with larger sample size is required to make significant conclusions regarding different tumor types.

Our preliminary findings on tumor subtypes are in agreement with the results obtained from published results [21,23]. We observed that the LUMA images showed higher vascular activity in the periphery of the tumor in comparison to the internal region. For TNBC, a significantly higher vascular activity could be detected internal to the tumor, compared to the surrounding tissue. For LUMB, while the tumor mass is small, there is a significant vascular activity in this region. Further studies with more data are needed to make more concrete analyses.

We also observed that photoacoustic images are not dependent on breast density. Figure 6 shows PA images of scattered fibroglandular tissue, heterogeneously dense tissue, and extremely dense breast cases, in comparison to their corresponding X-ray mammography images. While the X-ray mammograms show significant variation in images, the corresponding PA images are similar in intensity, vascular detail and imaging depth. These results show promise that our system can be used for mass screening procedures regardless of breast density.

While the results from DSM are promising, there are certain limitations for the current system. Firstly, coupling of smaller breast sizes with the top water tank is limited. This is the reason for fewer top breast data in comparison to the bottom. To address this issue, we are currently developing a rotatable system with sealed water tanks that can perform imaging in various planes, similar to X-ray mammography. This design will also address the limited view problem as the breast will be probed at different angles. In addition, the medio-lateral imaging will allow better access to breasts of smaller sizes and increase the field of view. Secondly, due to the low transducer frequency, the ultrasound image quality generated by the DSM is lower
in comparison to clinical US images. To improve this area, we are working on incorporating harmonic imaging in addition to spatial compounding in our system. Thirdly, our system is limited by the central frequency of our transducer. Currently, we are using a low central frequency of 2.25 MHz, which is useful for deep tissue imaging. Using a scanning head with higher central frequency, in the range of clinical US, can reveal microvascular structures, which may provide additional information of the tumor microenvironment. The increased tissue attenuation due to high frequency can be addressed through careful choice of the central frequency to find a good balance between spatial resolution and imaging depth. Lastly, in order to increase the field of view of our system, we can add round trip scanning with a lateral shift in the ultrasound transducer and optical fiber bundle between the two trips.

5. Conclusion

In this paper, we observed that most tumor breasts exhibited higher vascular activity, i.e., blood volume, contrast, and variation in PA intensity, in comparison to healthy breasts. Additionally, the PA results from tumor-bearing breast indicate the presence of vessels of larger caliber in the region. These results are promising as they agree with many previous studies [18,32,33]. If proven consistent, these results will go a long way in assessing tumors at various stages of development and also during treatment. More cases need to be studied to make further conclusions. Furthermore, we saw from PA and US overlaid images that tumor masses are more vascular in comparison to surrounding healthy tissue, and different subtypes exhibit different vascular behavior, in agreement with published literature [20,21]. These results reveal vascular characteristics along with morphological features. With further studies in the proposed directions, these conclusions can provide important insight with regards to tumor characteristics and progression, and prove to be very useful in reducing unnecessary biopsies.

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