

Full length article

Hypoxia-correlated functional photoacoustic tomography enhances breast tumor detection

Xin Tong^a , Cindy Z. Liu^a, Geng Ku^a, Stephanie Delos Santos^b, Marta Invernizzi^b, Lisa D. Yee^b, Lily L. Lai^b, Lihong V. Wang^{a,*}

^a Caltech Optical Imaging Laboratory, Andrew and Peggy Cherng Department of Medical Engineering, Department of Electrical Engineering, California Institute of Technology, 1200 E. California Blvd., MC 138-78, Pasadena, 91125, CA, USA

^b Department of Surgery, City of Hope Comprehensive Cancer Center, Duarte, 91010, CA, USA

ARTICLE INFO

Keywords:

Photoacoustic imaging
Tumor hypoxia
Breast cancer
Neoadjuvant chemotherapy

ABSTRACT

Breast photoacoustic tomography (PAT) enables noninvasive vascular imaging with high spatial resolution and optical contrast, but most prior studies have focused on static anatomy rather than functional dynamics. We introduce hypoxia-correlation functional PAT (hc-PAT), which leverages the abnormal vascular reactivity of malignant tumors. Participants underwent alternating breath-holding and normal breathing to induce transient systemic hypoxia, monitored by pulse oximetry. Simultaneous hc-PAT imaging was performed, and voxel-wise correlation with the oxygenation waveform generated functional maps. Malignant tumors showed significantly higher correlation coefficients than surrounding tissue, clearly delineating lesions consistent with magnetic resonance imaging (MRI) and tumor pathophysiology. Quantitative analysis revealed greater inter-breast asymmetry in malignant versus benign cases ($p \sim 0.014$). hc-PAT also sensitively tracked response to neoadjuvant chemotherapy, showing reduced hypoxia reactivity alongside MRI-confirmed tumor shrinkage. This pilot study demonstrates that hc-PAT can enhance breast cancer detection using endogenous functional contrast, suggesting the potential for sensitive, injection-free functional imaging that warrants validation in larger cohorts.

1. Introduction

Breast cancer is the second leading cause of cancer-related death in women, and reductions in mortality rely heavily on effective screening and early detection. However, accurate classification of breast abnormalities through imaging remains a persistent challenge [1]. Mammography, though widely used, exposes patients to ionizing radiation and has low sensitivity for detection of cancer in women with dense breast tissue (sensitivity < 50%) [2–4]. Ultrasonography (USG) is another common tool that complements mammography by revealing both structural and functional features of breast tissue. However, its reliability is highly operator-dependent, and conventional USG markers often fail to clearly separate malignant from benign lesions, leading to frequent biopsies or follow-ups imaging [5–7]. Recent innovations such as USG elastography and microvascular USG improve assessment of tissue stiffness and vascularity, yet they remain investigational and require further study in the clinical setting [8,9]. Breast magnetic resonance imaging (MRI) avoids ionizing radiation but demands intravenous contrast that carries risks including nephrotoxicity and can be problematic for claustrophobic patients or those with incompatible

breast implants [10–12]. Diffuse optical tomography provides sensitive functional contrast but suffers from poor spatial resolution [13,14]. Collectively, while current imaging modalities each offer meaningful advantages, their limitations continue to impede diagnostic confidence and patient comfort.

Photoacoustic tomography (PAT) has emerged as a powerful non-invasive imaging modality that combines optical excitation with ultrasonic detection [15,16]. In breast imaging, PAT enables whole-breast visualization with rich molecular contrast, high spatial and temporal resolution, and nonionizing optical penetration reaching depths of up to 4 cm [17–21]. PAT can selectively image various endogenous and exogenous contrast agents by tuning the illumination wavelength. For example, using hemoglobin as an intrinsic contrast agent in the near-infrared region enables the visualization of angiogenesis [22–25], which is critical in understanding tumor development and metastatic processes [26]. Beyond vascular anatomy, PAT can also capture functional signatures such as tumor hypoxia — where rapid metabolic demand outpaces blood supply — by quantifying oxy- and deoxy-hemoglobin signals [27,28]. Despite this potential, most clinical studies

* Corresponding author.

E-mail address: LVW@caltech.edu (L.V. Wang).

<https://doi.org/10.1016/j.pacs.2026.100897>

Received 21 April 2026; Received in revised form 8 August 2026; Accepted 6 October 2026

Available online 17 October 2026

2213-5979/© 2026 Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

to date have concentrated on static lesion characterization, such as vessel morphology or mean oxygen saturation, while largely neglecting dynamic assessments of vascular reactivity. Thus, the functional capabilities of PAT remain underutilized in breast cancer detection.

In this work, we adapt the established concept of a breath-hold hypoxia challenge with time-series correlation analysis — previously developed in dynamic diffuse optical tomography (DOT) and demonstrated preclinically with optical imaging for chemotherapy-response prediction [14,29] — to high-resolution photoacoustic tomography in human breast-cancer patients. We term this approach hypoxia-correlation functional PAT (hc-PAT), which uses a transient hypoxia challenge to distinguish tumor tissue from normal tissue based on vascular reactivity. Throughout this work, “hypoxia-correlated” (hc-) denotes the temporal correlation between a voxel’s single-wavelength (1064 nm) photoacoustic signal and the systemic arterial oxygenation (SpO_2) waveform measured by pulse oximetry during the breath-hold challenge; it reflects local vascular reactivity to a transient systemic hypoxic stimulus rather than an absolute measurement of local tissue oxygen saturation, which would require multi-wavelength spectral unmixing. The core idea is that malignant tumors, due to their abnormal vasculature, respond differently to a brief induced hypoxic stress than healthy tissue, producing functional contrast that hc-PAT can capture in real time. Participants underwent a series of short breath-holds (~10 s each) followed by deep-breath recovery, which induced cyclic drops and rebounds of 1–2 percentage points in systemic oxygen saturation as measured by a fingertip pulse oximeter. We monitored the blood oxygenation level continuously with a finger pulse oximeter, observing a cyclic drop and rebound in arterial oxygenation with each breath-hold. Concurrently, our hc-PAT system acquired sequential breast images to track hemodynamics throughout each cycle. To quantify these responses, we computed pixel-wise Pearson correlation coefficient between the local photoacoustic signal time courses and the global oxygenation waveform recorded from the oximeter. Tumor regions were expected to show stronger correlation coefficient — reflecting greater deoxygenation during hypoxia and rapid reoxygenation — due to their chaotic blood supply, whereas normal vasculature was hypothesized to buffer against brief hypoxic stress, resulting in weaker correlation coefficient with the systemic trend. Beyond distinguishing benign from malignant lesions, we further demonstrate that hc-PAT can monitor treatment response, capturing reductions in hypoxia reactivity during neoadjuvant chemotherapy in parallel with MRI-confirmed tumor shrinkage. This work establishes that PAT coupled with a simple physiological challenge can uncover dynamic functional biomarkers of breast cancer, opening a clinically translatable path toward safer, non-invasive, and more accurate breast imaging.

2. Results

2.1. System setup and functional imaging protocol

The hc-PAT protocol was implemented on a custom photoacoustic breast imaging system previously developed for fast, high-resolution human breast imaging [17,25]. The setup comprised a ring-shaped array of 512 ultrasonic transducers submerged in a water tank. During imaging, the participant lies prone on the imaging bed with one breast gently suspended in the water bath (Fig. 1a). A 1064 nm pulsed laser illuminated the breast from underneath (Fig. 1b). The photoacoustic signals generated by each laser pulse were detected by a surrounding full-ring ultrasonic transducer array.

Two imaging modes were implemented. In the 3D-PAT mode (Fig. 1c), the ring scanned elevationally across the breast within a single breath-hold (~13 s) to reconstruct a volumetric image. The system achieved ~0.25 mm spatial resolution and ~4 cm imaging depth [17]. In hc-PAT mode, the ring was fixed at the approximate tumor depth, enabling acquisition of cross-sectional time-lapse images at 10 Hz. Each

participant performed a guided breathing exercise consisting of a ~10-second breath-hold and then ~10 s of deep recovery breathing before the next cycle. This pattern was repeated 1–3 times to induce transient systemic hypoxia and re-oxygenation. During each breath-hold, the systemic oxygen saturation typically fell by 1–2 percentage points after a certain delay and then recovered during the subsequent breathing phase. Concurrently, our hc-PAT system acquired continuous time-series photoacoustic images (Fig. 1d), enabling pixel-wise assessment of breast tissue responses to the transient hypoxic challenge.

To quantify tissue response, we generated correlation coefficient maps by correlating the photoacoustic signal time sequence of each pixel with the global oxygenation waveform after image co-registration (Fig. 1e). High correlation coefficient means the voxel’s photoacoustic intensity varies in tandem with the blood oxygen level changes. Malignant tumor regions consistently exhibited higher correlation coefficient values, reflecting their strong synchronous response to transient hypoxia, whereas normal tissue showed lower correlation coefficient, remaining relatively stable despite mild systemic changes (Fig. 1f). The resulting correlation coefficient values were color-coded and overlaid on the anatomical PAT images, producing functional maps that highlighted oxygen-reactive regions (Fig. 1g). These functional PAT maps provided the foundation for our lesion detection approach.

2.2. Comparison with MRI images

In this pilot study, we imaged a small prospective cohort. We imaged five participants with malignant tumors. Fig. 2 compares our hc-PAT images to contrast-enhanced MRI in three representative participants with breast tumors. In Fig. 2a, results from a participant with left-breast invasive ductal carcinoma (IDC) show a distinct high-correlation coefficient hotspot on the hc-PAT map (left), which colocalizes with an enhancing lesion identified on MRI (right). This spatial correspondence confirms that hypoxia-response hc-PAT accurately highlighted the malignant region. Similarly, Fig. 2b and c depict two participants with right-breast IDCs, again demonstrating concordance between the hc-PAT functional hotspots and the MRI-confirmed lesions. The fourth participant did not have high-quality coronal MRI images available, and her axial MRI images are compared to the hc-PAT images in Fig. S1. The lesion was reported in the upper outer quadrant of the right breast, consistent with the hotspot observed in the hc-PAT heatmap (Fig. 3a). These examples demonstrate that hc-PAT can localize breast tumors with strong spatial concordance to MRI findings. Importantly, hc-PAT achieves this without the need for exogenous contrast agents — unlike MRI, which required gadolinium in these cases — and with minimal patient effort, relying only on a few brief breath-holds during the scan. To move beyond visual matching, we quantified the spatial agreement between hc-PAT and MRI after landmark-based registration (Methods). Across the malignant cohort, the lesion long-axis sizes from the two modalities were correlated (Fig. S5; Pearson $r = 0.60$, mean absolute difference 4.97 mm).

2.3. Comparison between malignant and benign lesions

Beyond comparison with MRI, we extended our analysis to additional participants with benign lesions to evaluate the diagnostic performance of hc-PAT. Fig. 3 summarizes the functional asymmetry between the affected and contralateral normal breast for each subject. In biopsy-confirmed cancers, the inter-breast difference in hc-PAT correlation coefficient was consistently greater than in benign cases such as cysts or fibroadenomas. Malignant tumors showed markedly elevated correlation coefficient in the tumor-bearing breast compared to the opposite side, reflecting their strong hypoxia-driven vascular response. In contrast, benign lesions exhibited little to no asymmetry, with correlation coefficient values resembling those of normal tissue.

We also quantitatively compared the hypoxia correlation feature with other commonly used structural features in PAT. The prespecified

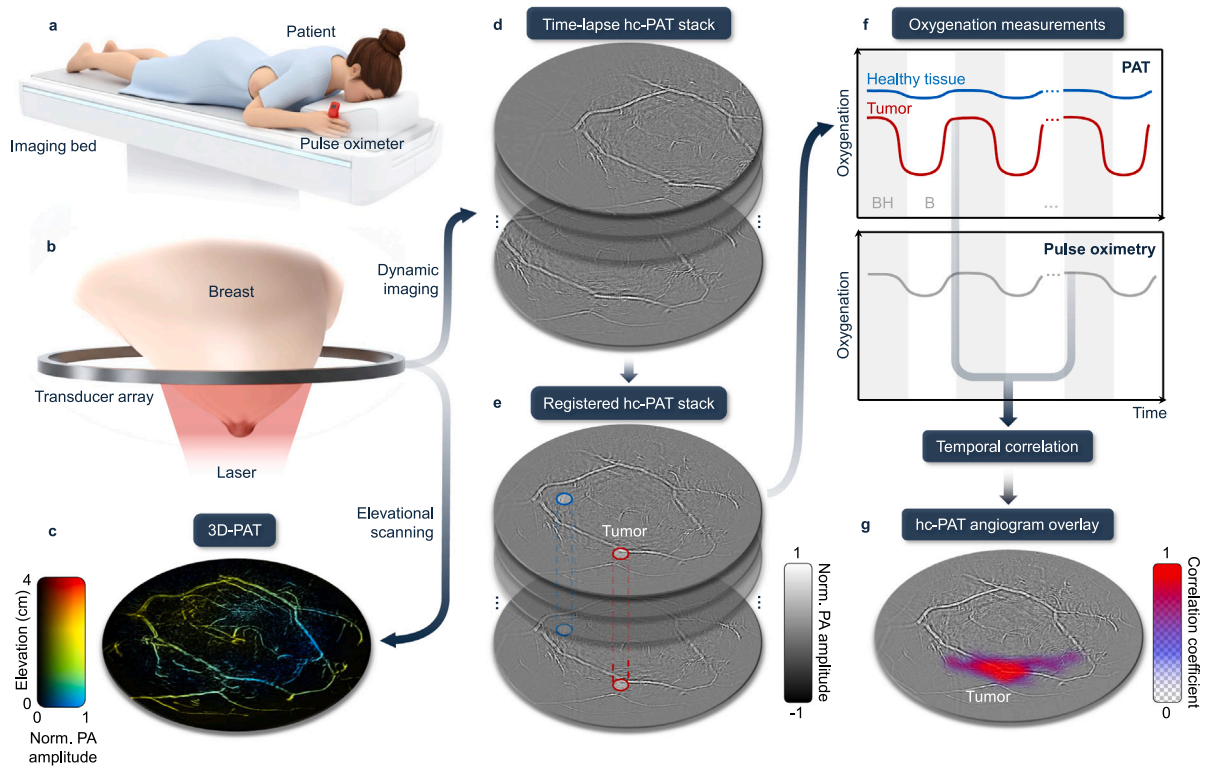


Fig. 1. Schematic of the hc-PAT protocol. **a**, Schematic of the hc-PAT imaging system. **b**, Enlarged view of the breast and transducer array in **a**, illustrating the position of the breast using an expanded laser beam within the water bath and its alignment relative to the full-ring transducer array. **c**, Depth-encoded maximum-amplitude-projection 3D-PAT image acquired through elevational scanning. **d–g**, hc-PAT data processing pipeline. The time-lapse cross-sectional images captured using the hc-PAT mode (**d**) were co-registered prior to extracting pixel-wise time sequences (**e**). Alternating breath-holding (BH, light gray) and breathing (B, white) cyclically varied systemic oxygen saturation, which was measured simultaneously by a fingertip pulse oximeter and PAT (**f**). Tumor vasculature (red) exhibited more pronounced signal fluctuations than normal vessels (blue, **g**). Norm., normalized.

primary endpoint was the ratio of the correlation coefficients between the affected and contralateral breasts, averaged per participant. Secondary endpoints included other imaging-derived features such as the ratio of photoacoustic amplitude and the ratio of vessel density between the two breasts, as well as other functional features such as the covariance ratio. Two-sided permutation tests were used to test the null hypothesis that the average inter-breast feature ratio in malignant cases is the same as that in benign cases. Malignant tumors tended to have higher photoacoustic amplitude and vessel density than normal breast or benign lumps [18,25], while those two features showed limited sensitivity in our cohort (Fig. 4a and b, raw vessel density maps can be found in Fig. S2). In contrast, the functional contrast derived from hypoxia correlation coefficient provided the clearest separation between malignant and benign lesions. For each participant, mean feature values from the affected breast were divided by those from the contralateral healthy breast. Statistical analysis confirmed that hypoxia-induced asymmetry was significantly greater in the malignant group (Fig. 4c; $p \sim 0.014$). In addition to the correlation coefficient, we evaluated three alternative functional features — (1) pixel-wise standard deviation, (2) average covariance, and (3) optimal pulse-oximetry–PAT delay — which yielded higher p -values and therefore lower discriminative power (Fig. S3). Furthermore, voxel-wise covariance maps were generated and demonstrated results consistent with those from correlation coefficient maps (Fig. S4). These results support the hypothesis that malignant tumors exhibit aberrant vascular reactivity to transient hypoxia, a hallmark not observed in benign lesions or normal tissue. Incorporating this functional biomarker could enhance the specificity of PAT for breast cancer diagnosis and help reduce false positives. We further verified that these findings are robust to acquisition choices. First, the inter-breast correlation-coefficient ratio showed no systematic dependence on the number of breath-hold cycles

(Spearman $\rho = -0.01$, $p = 1.0$); malignant lesions acquired with a single cycle still exhibited elevated correlation relative to the contralateral breast. Second, the malignant-versus-benign separation persisted across a range of fixed temporal lags, including zero lag (Fig. S7; at zero lag $p = 0.018$, Hedges' $g = 2.3$); because the same lag-selection procedure is applied identically to the affected and contralateral breasts and the endpoint is their ratio, the lag optimization improves sensitivity but cannot by construction inflate the malignant–benign difference.

2.4. Monitoring tumor responses from neoadjuvant chemotherapy

In addition to inter-patient comparisons, we evaluated the sensitivity of hc-PAT for monitoring tumor changes during neoadjuvant chemotherapy (NAC). A participant (patient 8) with left-breast IDC underwent serial PAT imaging sessions throughout her treatment, with results compared against contrast-enhanced MRI before and after NAC (Fig. 5), again showing good spatial correlation between hc-PAT and MRI images.

As shown in Fig. 5a–c, the tumor-associated hotspot in the hc-PAT heatmap became smaller and less intense through treatment, consistent with the marked reduction in tumor size observed on post-NAC MRI. To quantify these changes, we calculated the absolute inter-breast tile-wise differences in correlation coefficient values within the hotspot region (Fig. 5d). Recognizing that adjacent pixels are not statistically independent, we mitigated pseudoreplication by summarizing signals within spatially contiguous tiles and performing nonparametric Friedman permutation tests across imaging conditions at the tile level (details in Methods). This analysis yielded a p -value smaller than 0.001, confirming a significant reduction in tumor reactivity to hypoxia following treatment. These results demonstrate that hc-PAT can sensitively capture therapy-induced vascular normalization as well as tumor response during NAC within the same participant [30].

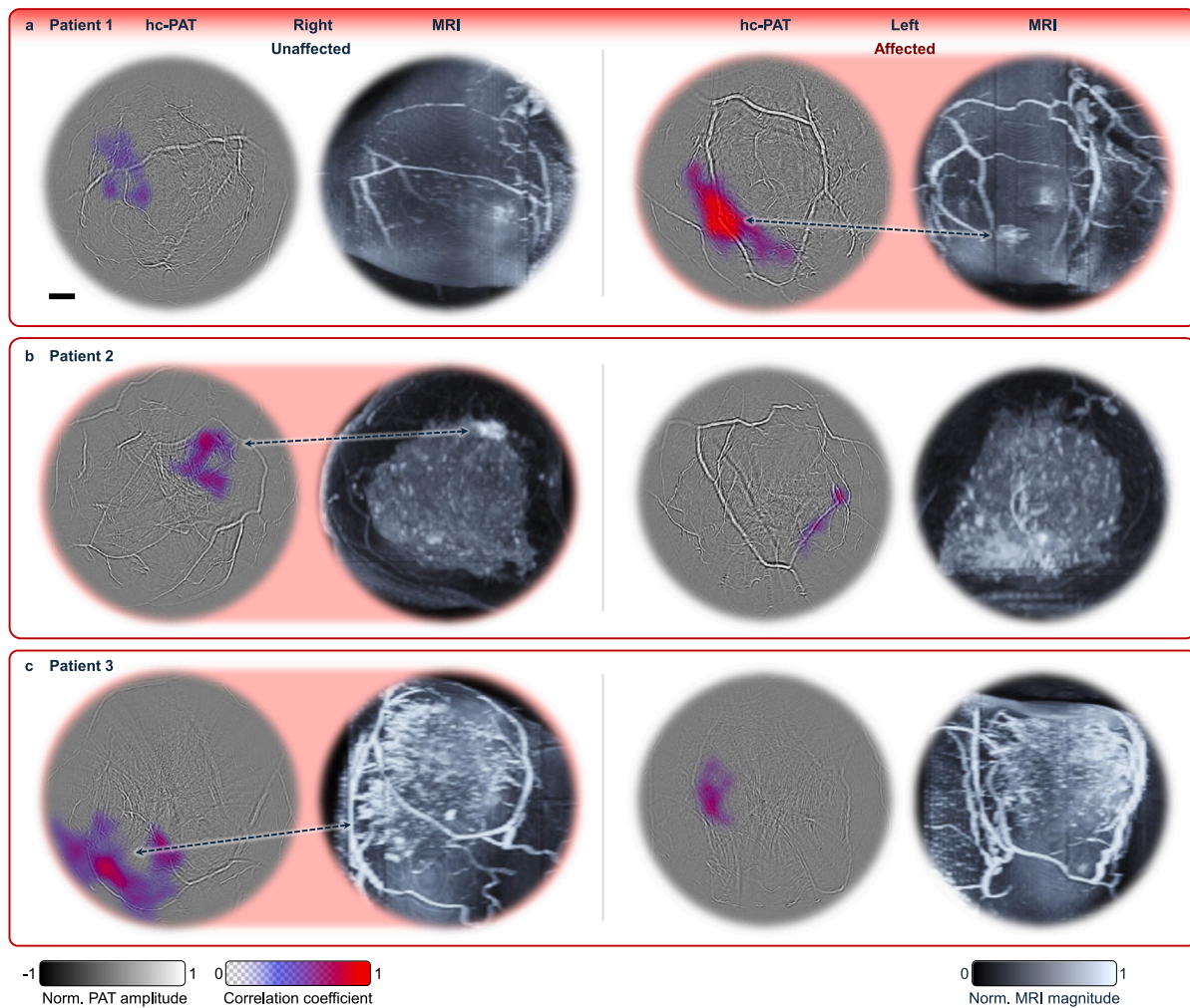


Fig. 2. Functional PAT versus MRI in three participants with (malignant) invasive ductal carcinomas. For each row (patient), hc-PAT correlation coefficient maps on the left overlaid on breast images show high-correlation coefficient hotspots at tumor locations. Contrast-enhanced MRI of the same breast on the right confirms enhancing lesions at the corresponding sites. Dashed arrows link the lesions between PAT and MRI images. Unaffected, contralateral breast without malignancy. Affected, breast with malignant tumor. Norm., normalized. Scale bar, 1 cm.

3. Discussion

This prospective pilot study, conducted in a small cohort, should be regarded as exploratory and hypothesis-generating. In this work, we developed a hc-PAT protocol that highlights malignant breast tumors by exploiting their abnormal vascular response to transient oxygen deprivation. The approach is non-invasive, requires no ionizing radiation or exogenous contrast, and derives diagnostic information from a simple breath-hold maneuver. Compared with mammography, hc-PAT provides high-resolution vascular contrast without compression or radiation risk. Compared with ultrasonography, it yields objective, quantitative biomarkers of vascular reactivity that are independent of operator skill. Compared with MRI, hc-PAT is low-cost, bedside-compatible, and intravenous contrast-free, yet produces lesion maps in strong spatial agreement with MRI findings. Importantly, whereas most breast PAT studies have emphasized static vessel anatomy or average oxygenation, our protocol introduces a dynamic, physiology-based functional dimension that amplifies tumor contrast. In particular, the ability to probe vascular reactivity in real time specific to the cancer distinguishes our approach and suggests a potentially clinically translatable path toward safer, faster, and more informative breast cancer imaging.

Our results leverage fundamental differences in tumor vascular physiology to achieve functional imaging contrast. Malignant tumors,

driven by pro-angiogenic signaling, develop vascular networks that are structurally and functionally abnormal [31–33]. Tumor vessels are frequently described as chaotic: they grow rapidly and irregularly, with variable diameters, blind ends, shunts, and excessive branching [34]. Tumor-associated endothelium is leaky and poorly supported by smooth muscle or pericytes, leading to impaired vascular tone and heterogeneous perfusion [33]. In healthy tissues, a drop in oxygen triggers vasodilation or blood flow redistribution to maintain oxygen delivery [35]. In tumors, this autoregulatory capacity is compromised—vessels cannot dilate appropriately or increase flow because of structural defects [14,29,33]. Moreover, tumors often exhibit hypoxia, where oxygenation fluctuates spontaneously due to transient vessel collapse or flow variations [36,37]. Additionally, cancer cells have elevated metabolic rates due to rapid proliferation and consume oxygen more quickly than normal tissue [31]. These inherent instabilities mean that a tumor's hemoglobin saturation might drop much more rapidly and deeply than normal tissue during a brief global hypoxic episode. Together, these features — disorganized vasculature, higher metabolic demands, loss of vasomotor control, and baseline oxygen debt — explain why tumors in our study displayed a more pronounced hemodynamic response to the breath-hold challenge than benign or normal tissues.

While the initial results are promising, several limitations should be noted. First, the current hc-PAT system employs a 2D ring trans-

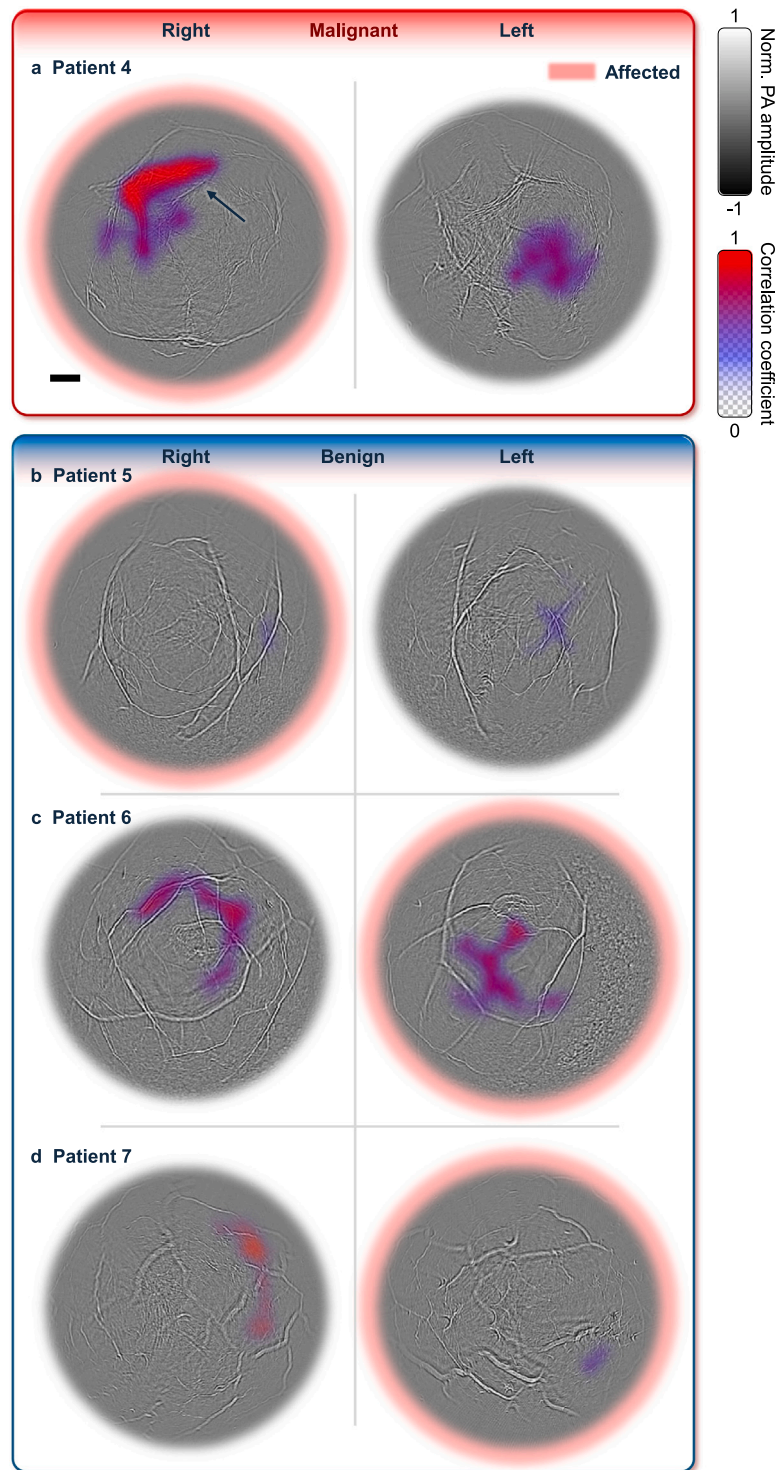


Fig. 3. Qualitative comparison of hypoxia-response between malignant and benign cases. **a**, hc-PAT-angiogram overlay images of both breasts from a participant with an invasive lobular carcinoma (a malignant lesion). **b–d**, hc-PAT-angiogram overlay images from three participants with benign breast lesions. The malignant case displays greater photoacoustic signal asymmetry between the affected and contralateral breast than benign cases. Norm., normalized. Scale bar, 1 cm.

ducer array positioned at a single central plane of the breast. The elevational resolution of the reconstructed 2D image is approximately 16 mm [17]. Tumors situated within this elevational range can be effectively captured, as for most participants in our cohort (Table S1); however, sensitivity and image quality are optimal only when the tumor depth is well aligned with the ring's imaging plane. As shown in Fig. S5, lesion size estimates from hc-PAT and MRI are generally

comparable, and the larger discrepancies observed in some participants are likely attributable in part to this depth mismatch. Second, oxygen saturation was monitored using a fingertip pulse oximeter, which provides only a global arterial measure and may not perfectly capture the timing of microvascular changes within the breast. Third, despite the small cohort size, the statistical analysis revealed a large effect size, with a Hedges' g of 3.6 (95% CI: [3.2, 10.6]), indicating

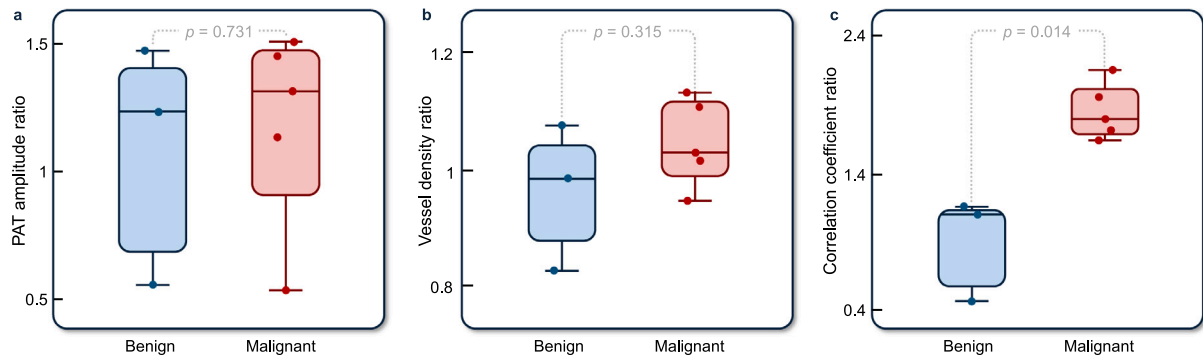


Fig. 4. Quantitative comparison of hypoxia-response between malignant and benign cases. **a**, Box plots of photoacoustic amplitude ratios between affected and contralateral breasts in participants with benign or malignant lesions. **b**, Box plots of vessel density ratios in the same cohort. **c**, Box plots of hypoxia correlation coefficient ratios, showing the clearest separation between malignant and benign groups. On each box, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers. $n_{\text{healthy}} = 3$, $n_{\text{malignant}} = 5$.

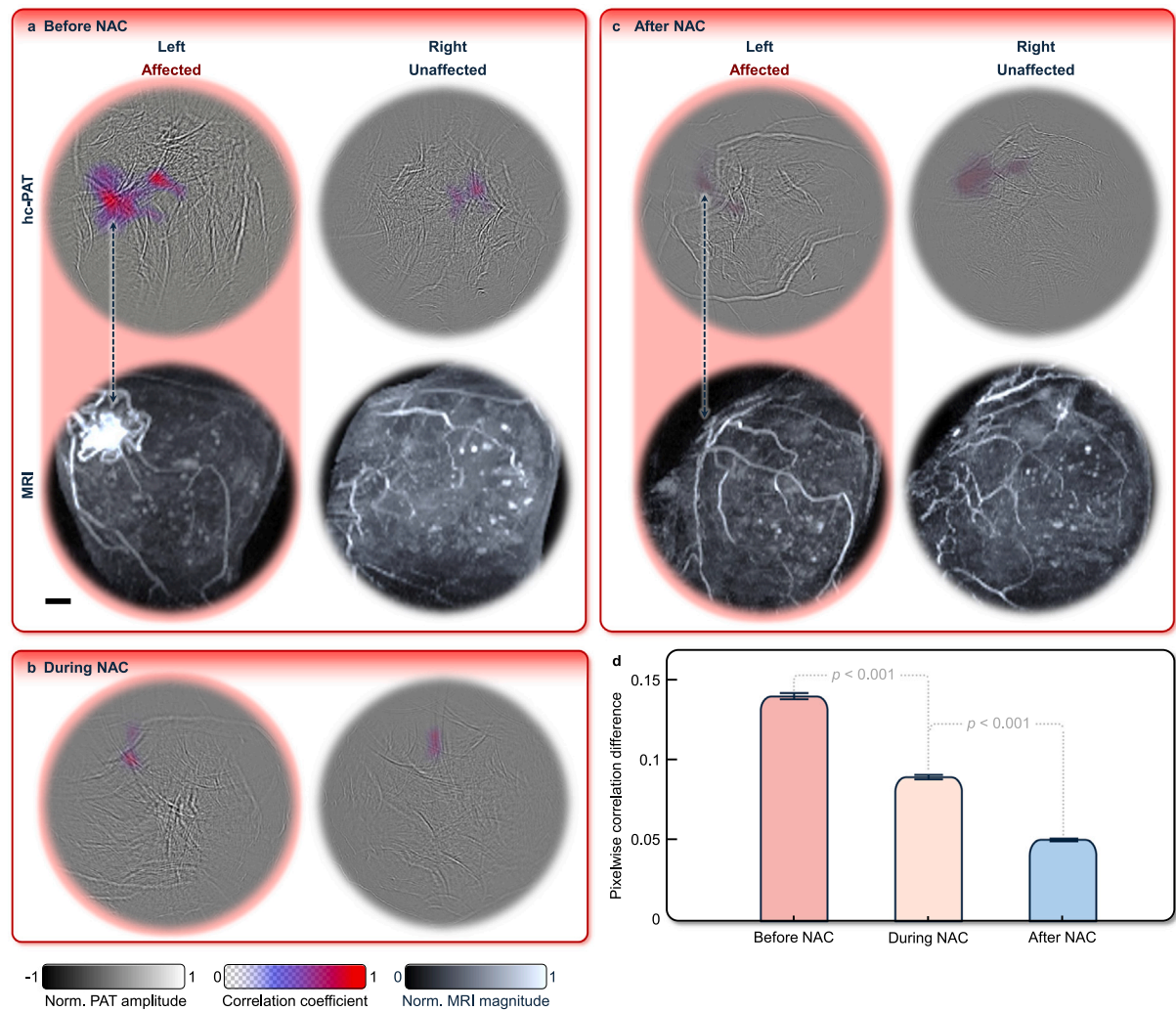


Fig. 5. Comparison of hypoxia-response in a malignant tumor before, during, and after neoadjuvant chemotherapy (NAC). **a–c**, hc-PAT-angiogram overlay images and corresponding contrast-enhanced MRI of both breasts acquired before (a), during (b), and after (c) NAC. Dashed arrows link the lesions between PAT and MRI images. Norm., normalized. Scale bar, 1 cm. **d**, Bar plot of pixel-wise absolute correlation coefficient differences in the tumor region between the affected and contralateral breast from the three visits, shown as mean $\pm$ standard errors of the mean. $n_{\text{before}} = n_{\text{during}} = n_{\text{after}} = 409$ denote the tile numbers in the segmented lesion areas.

a strong separation between the two groups. The corresponding two-sided permutation test yielded a p -value around 0.014, confirming statistical significance. This substantial effect size indicates high statistical power and supports the robustness of the hypoxia-correlation feature as a discriminative biomarker; however, larger cohorts will be valuable for further validation and generalization. More broadly, this is a small-sample, single-center prospective pilot study (5 malignant and 3 benign lesions); the results are exploratory and hypothesis-generating, and the wide confidence interval of the effect-size estimate reflects the limited cohort. Larger, multicenter studies with prespecified diagnostic endpoints, balanced benign and malignant representation, and diverse tumor subtypes will be required to establish diagnostic performance and generalizability before clinical adoption. Fourth, hc-PAT was acquired at a single wavelength (1064 nm). We chose 1064 nm because it offers the deepest optical penetration in breast tissue among clinically practical photoacoustic wavelengths (enabling whole-breast imaging up to ~ 4 cm on our system), because resolving the dynamics of a ~ 10 s breath-hold requires a high frame rate (10 Hz) that is incompatible with sequential multi-wavelength switching on our current single-laser hardware, and because the contrast mechanism is intentionally dynamic rather than spectroscopic. A single wavelength, however, cannot separate oxy- and deoxy-hemoglobin contributions; accordingly, the hc-PAT metric quantifies the temporal correlation between the single-wavelength signal and the systemic SpO_2 waveform and does not provide absolute local oxygen saturation. Multi-wavelength hc-PAT, which would additionally enable dynamic sO_2 mapping, is an important future direction. Fifth, in its current 2D implementation hc-PAT requires approximate prior knowledge of the lesion depth (from ultrasound or MRI) to position the single imaging plane, which limits its use as a fully stand-alone screening tool; volumetric 3D hc-PAT would image the whole breast without plane selection and eliminate this requirement. Sixth, the breath-hold paradigm was adapted to each participant's tolerance within standard-of-care visits rather than fully standardized; for future clinical use we recommend a standardized challenge of three cycles of a 15 s breath-hold followed by 15 s of recovery breathing (10 s/10 s for participants who cannot tolerate 15 s), with continuous pulse oximetry to confirm a target SpO_2 decline of at least 1–2 percentage points per cycle.

By integrating high-resolution optical absorption imaging with a simple physiological challenge, this work extends dynamic, physiology-based functional contrast — previously explored with lower-resolution diffuse optical methods — to high-resolution functional PAT of the breast. Relative to prior work, the specific contributions of this study are: (1) to our knowledge, the first clinical demonstration of a breath-hold hypoxia challenge combined with high-spatial-resolution (~ 0.25 mm) ring-array PAT in human breast-cancer patients, yielding voxel-wise reactivity maps that lower-resolution DOT cannot resolve; (2) a direct comparison showing that the hypoxia-correlation biomarker discriminates malignant from benign lesions more effectively than established structural PAT features in the same cohort; and (3) longitudinal evidence that hc-PAT tracks neoadjuvant-chemotherapy response within an individual patient. Tumors, with their chaotic and hypoxia-prone vasculature, manifest exaggerated responses that normal tissue does not. This added functional dimension has the potential to enhance both the sensitivity and specificity of breast cancer detection and breast cancer response to therapy when used alongside established imaging modalities. Several future directions emerge from this study. First, extending the system from single-slice to volumetric 3D PAT will allow whole-breast functional imaging. Second, larger clinical studies are required to rigorously evaluate diagnostic performance and to explore inter-patient variability across breast size, density, and tumor subtype. Finally, technical refinements — including multi-wavelength illumination and alternative physiological challenges such as hyperventilation — could further improve specificity and usability. Together, these advances will help translate hc-PAT into a practical and clinically impactful tool for breast cancer imaging.

4. Methods

4.1. System construction

In the PAT system, a 1064 nm laser beam from an Nd:YAG laser (LPY 7875-20, Litron Lasers, Ltd.) was expanded by an engineered diffuser (EDC-10, RPC Photonics, Inc.) to form a circular light beam. The laser radiant exposure (20.37 mJ cm^{-2} for 1064 nm) and irradiance ($407.44 \text{ mW cm}^{-2}$ for 1064 nm) were within the American National Standards Institutes (ANSI) safety limits for laser exposure [38]. For panoramic acoustic detection, a 512-element full-ring ultrasonic transducer array (Imasonic, Inc.; 2.25 MHz central frequency) was connected to four sets of 128-channel preamplifiers and data acquisition systems (SonixDAQ, Ultrasonix Medical ULC) placed around the water tank [17].

4.2. Study oversight

The human studies were completed under institutional approval and oversight by both California Institute of Technology (Committee for the Protection of Human Subjects, 23–1359, 24–1428, and 20–1040) and City of Hope National Medical Center (Institutional Review Board, 17315, 23909, and 19552). We are reporting breast PAT imaging results from three clinical studies: (1) women with locally advanced breast cancer initiating therapy with neoadjuvant chemotherapy (Caltech CPHS 23-1359/COH IRB 17315), (2) women with newly diagnosed breast cancer (Caltech CPHS 24-1428/COH IRB 23909), and (3) women with abnormal breast screening imaging BI-RADS 3–5 (Caltech CPHS 20-1040/COH IRB 19552). The clinical studies were conducted in accordance with institutional guidelines. Study participants were informed of the investigational nature of the study and provided informed consent.

4.3. Patient selection and exclusion criteria

For participants associated with Caltech CPHS 20-1040/COH IRB 19552, all recruited participants met the following inclusion criteria: (1) women newly identified to have abnormal mammograms, breast ultrasound and/or breast MRI as part of breast cancer screening, with BI-RADS 3–5 breast lesions for which diagnostic biopsy (BI-RADS 4–5) or close interval radiologic follow-up (BI-RADS 3) is recommended; (2) >18 years of age; (3) able to understand and willing to sign a written informed consent document; (4) willing and able to undergo photoacoustic imaging prior to the standard of care biopsy procedure for a BI-RADS 4 or 5 breast imaging. The exclusion criteria included (1) weight exceeding 300 lbs (weight limit of the steps to the PAT examination table); (2) pregnancy or lactation; (3) uncontrolled intercurrent illness including, but not limited to, ongoing or active infection of the breast and/or axilla, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements; (4) use of photosensitizing medication.

For participants associated with Caltech CPHS 23-1359 and 24-1428/COH IRB 17315 and 23909, all recruited participants met the following inclusion criteria: (1) women newly diagnosed with breast cancers; (2) ≥ 18 years of age; (3) able to understand and willing to sign a written informed consent document; (4) participants must have intact skin in the area that is to be imaged (i.e., no skin cuts, open wounds, ulcers). The exclusion criteria included (1) weight exceeds 300 lbs; (2) pregnancy; (3) uncontrolled intercurrent illness including, but not limited to, ongoing or active infection of the breast and/or axilla, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.4. Standard PAT imaging procedure

Breast imaging was performed at City of Hope in a dedicated human imaging room installed with privacy curtains. Prior to PAT imaging, the imaging bed and the imaging system were thoroughly sanitized using disinfecting wipes. The examination table was covered by single-use paper discarded after each use. Participants were provided privacy to change to hospital gowns. During PAT imaging, two to three female study coordinators assisted the participant in a private space enclosed by curtains. All other researchers were outside the private space to operate the PAT device. The participant was positioned prone, with one breast placed in the preheated 35 °C water tank through a large aperture in the bed top. Prior to hc-PAT imaging, the approximate tumor depth was known from clinical ultrasound or MRI. If the lesion was located near the central plane, the imaging ring was positioned at the breast center (approximately 2.5 cm from the nipple). For tumors known to deviate significantly from the mid-plane, the ring position was adjusted accordingly to align the imaging depth with the tumor location and optimize sensitivity. A pulse oximeter (EMAY EMO-80) was put on the participant's thumb to monitor her oxygenation level during imaging. The number and duration of breath-hold cycles were adapted to each participant's tolerance within the available clinical session; as a pilot study integrated into standard-of-care visits, a fully uniform stimulation paradigm was not enforced. Per-participant acquisition parameters (number of cycles, breath-hold duration, and SpO₂ fluctuation magnitude) are summarized in Table S2. Because the 2D ring images only a single elevational plane, the imaging depth was set using the lesion depth from prior ultrasound or MRI; hc-PAT in its current 2D form therefore depends on approximate prior localization, as discussed in the limitations.

4.5. Image reconstruction and post-processing

All photoacoustic images were reconstructed using the half-time universal back-projection (UBP) algorithm [17,39]. The 2D and 3D modes employ two distinct UBP formulations rather than slice stacking. In the 3D mode, the ring array scans the breast elevationally and the PA signals from all elevational steps are back-projected simultaneously into the 3D volume; to accommodate the elevational acoustic divergence, the 3D-UBP weights the back-projected signals by elevational divergence angle and places virtual transducers at the Fresnel-Fraunhofer transition to reconstruct objects in the Fraunhofer zone, improving the elevational resolution from ~16 mm (2D) to ~5.6 mm (3D) [17]. This 3D-UBP volume (Fig. 1c) was used only for anatomical and vascular visualization; all quantitative hc-PAT correlation analyses used the 2D fixed-plane reconstructions described below. In 2D mode, time-domain signals from each laser pulse were back-projected onto a 120 mm × 120 mm field of view with 0.25 mm pixels, assuming a uniform speed of sound of 1500 m/s. Motion artifacts were corrected by registering each frame to the first frame of its sequence using a diffeomorphic demons algorithm (MATLAB `imregdemons`) with an accumulated-field smoothing parameter of 5. Amplitude envelopes were extracted from each registered frame via a monogenic Riesz transform and mildly denoised with separable 3D Gaussian smoothing ($\sigma \approx [0.1, 0.1, 0.01]$ in pixel/frame units). Each pixel's temporal trace was low-pass filtered using a 4th-order Butterworth filter (cutoff 0.2) before computing correlations with the SpO₂ curve measured during the hypoxia-challenge sequence. The optimal temporal lag was determined by scanning delays between -10–10 s and selecting the lag that maximized the mean of the top 100 correlation coefficients. Scanning a lag accounts for the physiological transit-time delay between a systemic oxygenation change and its appearance both at the fingertip oximeter and within the breast; the optimal lags obtained were small and physiologically plausible (a few seconds; Fig. S6). The same lag-selection procedure was applied identically to the affected and contralateral

breasts, so it cannot bias the inter-breast ratio used for malignant-benign discrimination, and the discrimination is robust across fixed lags (Fig. S7). Correlation maps were denoised using a 10 × 10 median filter and thresholded at mean + standard deviation to define functional hotspots within a manually determined breast mask.

4.6. Co-registration between MRI and PAT images

The Gd-MRI images were acquired and shared as DICOM files. We used the built-in function `dicomread` in MATLAB to load the files as volumetric images to correlate with PAT images. The MRI images were then rendered as coronal maximum intensity projections (MIPs) to be shown in Figs. 2 and 5. While the two images generally correlate well, small differences remain primarily from tissue deformation, with the breast fully dependent in MRI and slightly compressed in PAT. To quantify spatial agreement rather than rely on visual matching, the coronal MRI MIP was aligned to the corresponding hc-PAT en-face image using a similarity transform (rigid rotation and translation plus isotropic scaling) anchored on common landmarks—the nipple position, the breast outline, and major superficial vessels visible in both modalities. Exact deformable registration is not attainable because of the different breast geometries and image-formation physics; the landmark-based registration and the resulting lesion-size agreement (Fig. S5) therefore provide an objective, if approximate, measure of concordance.

4.7. Statistical analysis

The prespecified primary endpoint was the ratio of correlation coefficients between the affected and contralateral breasts, averaged per participant, reflecting inter-breast asymmetry in hypoxia-induced vascular reactivity. Secondary endpoints included the covariance ratio, photoacoustic amplitude ratio, and vessel density ratio, which served to assess complementary structural and functional contrasts.

To evaluate group differences between participants with malignant and benign lesions, two-sided permutation tests ($N = 1000$ iterations) were performed for each endpoint to compute p -values, ensuring robustness against small-sample bias. In addition, effect size was quantified using Hedges' g , which incorporates a small-sample correction. For the primary endpoint, Hedges' g was estimated at 3.6, with a bootstrap 95% confidence interval [3.2, 10.6], indicating a large separation between malignant and benign groups and effect size despite the limited cohort size.

To compare pixel intensity distributions across three imaging conditions while accounting for spatial correlation, we applied a tile-based nonparametric permutation framework. ROI pixels were divided into contiguous 10 × 10 tiles, excluding those with <30 ROI pixels. Mean values per condition were computed for each retained tile, yielding repeated measures across conditions. A Friedman statistic was calculated using tiles as sampling units. Its null distribution was generated from 1000 within-tile label permutations, with p -values estimated from the proportion of permuted statistics observed. Pairwise differences were tested using permutation-based t -like statistics with $\max\{|T|\}$ correction. Statistical significance was set at $\alpha = 0.05$.

The two scientific questions required different sampling units. Benign-versus-malignant discrimination is a between-participants comparison, so the unit is one summary statistic per participant (the inter-breast feature ratio), which avoids pseudoreplication across the many spatially correlated voxels within a breast. Neoadjuvant-chemotherapy monitoring is a within-participant longitudinal comparison in a single patient across visits, for which a single value per visit would provide no measure of spatial variability; we therefore used spatially contiguous tiles as repeated-measures units (Friedman permutation test), again chosen to mitigate the pseudoreplication that would arise from treating adjacent voxels as independent. Thus both analyses follow the same principle — an appropriate independent unit — but differ in unit because the questions differ.

CRediT authorship contribution statement

Xin Tong: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cindy Z. Liu:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. **Geng Ku:** Methodology, Investigation. **Stephanie Delos Santos:** Writing – review & editing, Investigation. **Marta Invernizzi:** Writing – review & editing, Investigation. **Lisa D. Yee:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Lily L. Lai:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization. **Lihong V. Wang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the California Institute of Technology Committee for the Protection of Human Subjects, City of Hope National Medical Center Institutional Review Board. (Approval No. Caltech: 23–1359, 24–1428, and 20–1040; City of Hope: 17315, 23909, and 19552)

Funding

This project has been made possible in part by National Institutes of Health grants R01 CA282505 (COH), UG3 DA065155, and U01 EB029823 (BRAIN3 Initiative). C. L. was sponsored by the National Institutes of Health grants NIGMS T32 GM008042 and NIGMS T32 GM152342.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lihong V. Wang reports financial support was provided by National Institutes of Health. Lily L. Lai reports financial support was provided by National Institutes of Health. Lihong V. Wang has patent pending to California Institute of Technology. L.V.W. has a financial interest in Microphotoacoustics, Inc., CalPACT, LLC, and Union Photoacoustic Technologies, Ltd., which, however, did not support this work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.pacs.2026.100897>.

Data availability

All data used in this study are available from the corresponding author upon reasonable request. The custom reconstruction and post-processing algorithms are described in detail in Methods and Ref. [39]. We have opted not to make other computer codes publicly available because the code is proprietary and used for other projects and potentially licensed technologies.

References

- [1] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, 2022, CA: Cancer J. Clin. 72 (1) (2022).
- [2] T.M. Kolb, J. Lichy, J.H. Newhouse, Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations, Radiology 225 (1) (2002) 165–175.
- [3] B. Wa, Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer, Radiology 233 (2004) 830–849.
- [4] M. von Euler-Chelpin, M. Lillholm, I. Vejborg, M. Nielsen, E. Lynge, Sensitivity of screening mammography by density and texture: a cohort study from a population-based screening program in Denmark, Breast Cancer Res 21 (1) (2019) 111.
- [5] C.D. Lehman, C. Isaacs, M.D. Schnall, E.D. Pisano, S.M. Ascher, P.T. Weatherall, D.A. Bluemke, D.J. Bowen, P.K. Marcom, D.K. Armstrong, et al., Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study, Radiology 244 (2) (2007) 381–388.
- [6] V. Corsetti, N. Houssami, A. Ferrari, M. Ghirardi, S. Bellarosa, O. Angelini, C. Bani, P. Sardo, G. Remida, E. Galligioni, et al., Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost, Eur. J. Cancer 44 (4) (2008) 539–544.
- [7] S. Raza, S.A. Chikarmane, S.S. Neilsen, L.M. Zorn, R.L. Birdwell, BI-RADS 3, 4, and 5 lesions: value of US in management—follow-up and outcome, Radiology 248 (3) (2008) 773–781.
- [8] C. Errico, J. Pierre, S. Pezet, Y. Desailly, Z. Lenkei, O. Couture, M. Tanter, Ultrafast ultrasound localization microscopy for deep super-resolution vascular imaging, Nature 527 (7579) (2015) 499–502.
- [9] R.M. Sigrist, J. Liao, A. El Kaffas, M.C. Chammas, J.K. Willmann, Ultrasound elastography: review of techniques and clinical applications, Theranostics 7 (5) (2017) 1303.
- [10] I. Eshed, C.E. Althoff, B. Hamm, K.-G.A. Hermann, Claustrophobia and premature termination of magnetic resonance imaging examinations, J. Magn. Reson. Imaging: Off. J. Int. Soc. Magn. Reson. Med. 26 (2) (2007) 401–404.
- [11] O.P. Faris, M.J. Shein, Government viewpoint: US food & drug administration: pacemakers, ICDs and MRI, Pacing Clin. Electrophysiol. 28 (4) (2005) 268–269.
- [12] M.A. Perazella, Gadolinium-contrast toxicity in patients with kidney disease: nephrotoxicity and nephrogenic systemic fibrosis, Curr. Drug Saf. 3 (1) (2008) 67–75.
- [13] D.R. Leff, O.J. Warren, L.C. Enfield, A. Gibson, T. Athanasiou, D.K. Patten, J. Hebden, G.Z. Yang, A. Darzi, Diffuse optical imaging of the healthy and diseased breast: a systematic review, Breast Cancer Res. Treat. 108 (1) (2008) 9–22.
- [14] M.L. Flexman, H.K. Kim, J.E. Gunther, E.A. Lim, M.C. Alvarez, E. Desperito, K. Kalinsky, D.L. Hershman, A.H. Hielscher, Optical biomarkers for breast cancer derived from dynamic diffuse optical tomography, J. Biomed. Opt. 18 (9) (2013) 096012.
- [15] L.V. Wang, Multiscale photoacoustic microscopy and computed tomography, Nat. Photonics 3 (9) (2009) 503–509.
- [16] L. Lin, L.V. Wang, The emerging role of photoacoustic imaging in clinical oncology, Nat. Rev. Clin. Oncol. 19 (6) (2022) 365–384.
- [17] L. Lin, P. Hu, J. Shi, C.M. Appleton, K. Maslov, L. Li, R. Zhang, L.V. Wang, Single-breath-hold photoacoustic computed tomography of the breast, Nat. Commun. 9 (1) (2018) 2352.
- [18] L. Lin, X. Tong, P. Hu, M. Invernizzi, L. Lai, L.V. Wang, Photoacoustic computed tomography of breast cancer in response to neoadjuvant chemotherapy, Adv. Sci. 8 (7) (2021) 2003396.
- [19] L. Lin, P. Hu, X. Tong, S. Na, R. Cao, X. Yuan, D.C. Garrett, J. Shi, K. Maslov, L.V. Wang, High-speed three-dimensional photoacoustic computed tomography for preclinical research and clinical translation, Nat. Commun. 12 (1) (2021) 882.
- [20] S. Han, H. Lee, C. Kim, J. Kim, Review on multispectral photoacoustic analysis of cancer: thyroid and breast, Metabolites 12 (5) (2022) 382.
- [21] M. Dantuma, F. Lucka, S. Kruitwagen, A. Javaherian, L. Alink, R.P. van Meerdervoort, M. Nanninga, T. Root, B. De Santi, J. Budisky, et al., Fully three-dimensional sound speed-corrected multi-wavelength photoacoustic breast tomography, 2023, arXiv preprint arXiv:2308.06754.
- [22] N. Weidner, J.P. Semple, W.R. Welch, J. Folkman, Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma, N. Engl. J. Med. 324 (1) (1991) 1–8.
- [23] A. Longatto Filho, J.M. Lopes, F.C. Schmitt, Angiogenesis and breast cancer, J. Oncol. 2010 (1) (2010) 576384.
- [24] A.R. Reynolds, I.R. Hart, A.R. Watson, J.C. Welti, R.G. Silva, S.D. Robinson, G. Da Violante, M. Gourlaouen, M. Salih, M.C. Jones, et al., Stimulation of tumor growth and angiogenesis by low concentrations of RGD-mimetic integrin inhibitors, Nature Med. 15 (4) (2009) 392–400.
- [25] X. Tong, C.Z. Liu, Y. Luo, L. Lin, J. Dzubnar, M. Invernizzi, S. Delos Santos, Y. Zhang, R. Cao, P. Hu, et al., Panoramic photoacoustic computed tomography with learning-based classification enhances breast lesion characterization, Nat. Biomed. Eng. (2025) 1–17.

- [26] J. Folkman, Role of angiogenesis in tumor growth and metastasis, in: *Seminars in Oncology*, Elsevier, 2002, pp. 15–18.
- [27] P. Vaupel, S. Briest, M. Höckel, Hypoxia in breast cancer: pathogenesis, characterization and biological/therapeutic implications, *Wien. Med. Wochenschr.* 152 (13–14) (2002) 334–342.
- [28] D.M. Gilkes, G.L. Semenza, Role of hypoxia-inducible factors in breast cancer metastasis, *Future Oncol.* 9 (11) (2013) 1623–1636.
- [29] S. Lee, J.G. Kim, Breast tumor hemodynamic response during a breath-hold as a biomarker to predict chemotherapeutic efficacy: preclinical study, *J. Biomed. Opt.* 23 (4) (2018) 048001.
- [30] S. Guelfi, K. Hodivala-Dilke, G. Bergers, Targeting the tumour vasculature: from vessel destruction to promotion, *Nat. Rev. Cancer* 24 (10) (2024) 655–675.
- [31] R.A. Weinberg, *The Biology of Cancer*, W.W. Norton & Company, New York, 2006.
- [32] J.D. Martin, G. Seano, R.K. Jain, Normalizing function of tumor vessels: progress, opportunities, and challenges, *Annu. Rev. Physiol.* 81 (1) (2019) 505–534.
- [33] J.C. Forster, W.M. Harriss-Phillips, M.J. Douglass, E. Bezak, A review of the development of tumor vasculature and its effects on the tumor microenvironment, *Hypoxia* (2017) 21–32.
- [34] R.K. Jain, Molecular regulation of vessel maturation, *Nature Med.* 9 (6) (2003) 685–693.
- [35] P.C. Johnson, Autoregulation of blood flow, *Circ. Res.* 59 (5) (1986) 483–495.
- [36] P. Vaupel, K. Schlenger, C. Knoop, M. Höckel, Oxygenation of human tumors: evaluation of tissue oxygen distribution in breast cancers by computerized O₂ tension measurements, *Cancer Res.* 51 (12) (1991) 3316–3322.
- [37] R.C. Perez, D. Kim, A.W. Maxwell, J.C. Camacho, Functional imaging of hypoxia: PET and MRI, *Cancers* 15 (13) (2023) 3336.
- [38] ANSI Z136.1 Committee, *American National Standard for Safe Use of Lasers*, ANSI Z136.1-2022 ed., Laser Institute of America, Orlando, FL, 2022, ANSI Z136.1-2022.
- [39] M. Xu, L.V. Wang, Universal back-projection algorithm for photoacoustic computed tomography, *Phys. Rev. E* 71 (1) (2005) 016706.



Xin Tong is a Ph.D. student in Medical and Electrical Engineering at the California Institute of Technology (Caltech). He obtained his Master of Science in Medical Engineering from the same university and his Bachelor of Science in Applied Physics from Peking University, China. He is committed to exploring the fields of optical imaging and imaging processing, with a particular focus on non-invasive photoacoustic computed tomography and quantum imaging.



Cindy Z. Liu is a graduate student in the Caltech Optical Imaging Laboratory at the California Institute of Technology. She received her B.S. in Biomedical Computation at Stanford University and MPhil in Advanced Computer Science at the University of Cambridge. She is currently a MD/PhD student in the UCLA-Caltech Medical Scientist Training Program. Her research interests include photoacoustic imaging and machine learning methods for biomedical imaging and diagnosis.



Geng Ku is a staff scientist in the Caltech Optical Imaging Laboratory at the California Institute of Technology. He received the B.S. and M.S. degrees from Huazhong University of Science and Technology, Wuhan, China, and the Ph.D. degree from the Department of Biomedical Engineering, Texas A&M University, College Station. His research interests include laser-based photoacoustic tomography and microwave-based thermoacoustic tomography.



Stephanie Delos Santos is a clinical research assistant at City of Hope National Medical Center. She holds a B.S. in Neuroscience from University of California, Riverside. Her current research projects include photoacoustic imaging in the setting of newly diagnosed breast cancer.



Marta Invernizzi is a staff scientist at City of Hope specializing in clinical trials using imaging modalities. She designs clinical protocols, supports implementation and execution, collaborates with external institutions. She holds a PhD-equivalent qualification in Medical Physics (Italian residency program) from Università degli Studi di Milano, with MS and BS degrees in Physics and research experience.



Lisa D. Yee, MD, FACS, Professor, Division of Breast Surgery and Vice Chair of Research, Department of Surgery, City of Hope, Duarte, CA is a breast surgical oncologist with clinical and research interests in breast cancer prevention and symptom intervention and novel biomarkers of breast cancer risk for clinical applications.



Dr. Lily L. Lai completed undergraduate studies at Harvard before entering medical school and finishing residency at UC San Diego School of Medicine. After fellowship training in Surgical Oncology, Dr. Lai became faculty at the City of Hope, a NCCN Comprehensive Cancer Center. She specializes in Breast and Colorectal Cancers. She is an NIH-funded researcher with a focus creative adaptation of existing and new technology for cancer. In addition to her clinical work and research, Dr. Lai is the Vice Chair of Education in the Department of Surgery as well as the Surgical Oncology Fellowship Program Director.



Lihong V. Wang is Bren Professor of Medical Engineering and Electrical Engineering, Andrew and Peggy Cherng Medical Engineering Leadership Chair, and Executive Officer (Department Chair) of Medical Engineering at California Institute of Technology. He has published 625 peer-reviewed journal articles and has delivered 647 keynote, plenary, or invited talks. His book entitled “Biomedical Optics: Principles and Imaging,” won the 2010 Joseph W. Goodman Book Writing Award. He also edited the first book on photoacoustic tomography. His Google Scholar h-index and citations have reached 167 and 121 K, respectively, and he is ranked #1 in citations in optics and #4 in nuclear medicine and medical imaging according to Stanford/Elsevier. He received the NSF CAREER, NIH FIRST, and NIH Director’s Pioneer awards, among many others. An honorary doctorate was conferred on him by Lund University, Sweden. He was inducted into the National Academy of Inventors, the National Academy of Engineering, and the National Academy of Medicine.