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Quantitative analysis of vascular properties derived from ultrafast DCE-MRI to discriminate malignant and benign breast tumors

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Abstract

Purpose: We propose a novel methodology to integrate morphological and functional information of tumor-associated vessels to assist in the diagnosis of suspicious breast lesions.

Theory and Methods: Ultrafast, fast, and high spatial resolution DCE-MRI data were acquired on 15 patients with suspicious breast lesions. Segmentation of the vasculature from the surrounding tissue was performed by applying a Hessian filter to the enhanced image, to generate a map of the probability for each voxel to belong to a vessel. Summary measures were generated for vascular morphology, as well as the inputs and outputs of vessels physically connected to the tumor. The ultrafast DCE-MRI data was analyzed by a modified Tofts model to estimate the bolus arrival time, K^{trans} (volume transfer coefficient), and v_p (plasma volume fraction). The measures were compared between malignant and benign lesions *via* the Wilcoxon test, and then incorporated into a logistic ridge regression model to assess their combined diagnostic ability.

Results: A total of 24 lesions were included in the study (13 malignant and 11 benign). The vessel count, K^{trans} , and v_p showed significant difference between malignant and benign lesions ($P = 0.009, 0.034$ and 0.010 , AUC = 0.76, 0.63 and 0.70, respectively). The best multivariate logistic regression model for differentiation included the vessel count and bolus arrival time (AUC = 0.91).

Conclusion: This study provides preliminary evidence that combining quantitative characterization of morphological and functional features of breast vasculature may provide an accurate means to diagnose breast cancer.

Keywords

(6) cancer; registration; segmentation; perfusion; pharmacokinetics; biomarker

Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) involves the serial acquisition of heavily T_1 -weighted images acquired before, during, and after the injection of a paramagnetic contrast agent (1). Both semi-quantitative and quantitative analysis of DCE-MRI have been shown to provide important insights in both the diagnostic (2–4) and prognostic (5–7) settings for breast cancer. Within the diagnostic setting, the sensitivity of DCE-MRI has been reported as 88% to 100% (8,9), but with a variable specificity of 63% to 96% (8,9). Thus, it is of great importance to develop new MRI acquisition and analysis methods that can yield improved biomarkers with higher specificity for the diagnosis of suspicious breast lesions. Intimately related to this problem is the issue of balancing the competing acquisition demands of obtaining data acquired at both high spatial and high-temporal resolution.

In the standard-of-care setting, great emphasis is placed on collecting DCE-MRI data at very high spatial resolution, thereby necessitating low temporal resolution (e.g., 60–120 sec). Several studies have indicated that high spatial resolution data enable quantitative characterization of vascular features which can then assist in diagnosis (10–19). In general, these efforts are focused on manual evaluation of ipsilateral breast vascularity, bilateral symmetry, and vessels adjacent to the suspicious lesion. Importantly, the majority of the current literature on the topic employs analysis of maximum intensity projections. This naturally eliminates information describing the vascular structure in 3D, and may even be misleading by suggesting certain vessels are in contact with the lesion itself (20). There are, however, few studies focused on methods for automatically identifying (in 3D) the vessels that directly feed or drain the suspicious lesion. Furthermore, there is a paucity of studies investigating the synthesis of vessel architecture (i.e., morphology) with the results of a quantitative DCE-MRI analysis (i.e., function).

While high spatial resolution can provide exquisite characterization of morphology, it precludes accurate quantification of pharmacokinetic parameters that are important indicators of malignancy, and does not allow tracking of the contrast media bolus as it propagates through arteries and veins. The advantages of high temporal resolution DCE-MRI has been demonstrated by several groups (21–27), including a reduction of error in pharmacokinetic modeling (21–22) and increased performance in detecting pre-invasive cancers in the early phase of contrast agent uptake (23–24). Analysis of ultrafast DCE-MRI also has the potential to evaluate the vascular input and output of breast tumors (25), and to discriminate benign from malignant lesions (26).

In this contribution, we propose a novel methodology/framework that combines vessel detection with analysis of ultrafast DCE-MRI data to integrate both morphological and functional information of tumor associated vessels to assist in the diagnosis of suspicious breast lesions. Using high spatial resolution data, we have developed algorithms to

automatically 1) segment the breast vasculature in 3D, 2) identify and count individual tumor feeding and draining vessels, and 3) compute vessel number and tortuosity. We then integrate these methods with kinetic parameters available from ultrafast DCE-MRI data analysis and a logistic ridge regression model to provide a more complete characterization of breast lesions in the diagnostic setting.

Methods

Patients and lesions

Patients were recruited as part of an ongoing IRB-approved study. 18 women with BIRADS (Breast Imaging Reporting and Data System) 4 or 5 lesions identified on screening mammography, and with category C or D breast density, were approached to receive a research MRI prior to biopsy (these women would not normally qualify for a clinical MRI prior to biopsy). Images from three patients were excluded because no abnormal enhancement was found (all 3 cases had benign biopsy findings). The remaining 15 patients (median age = 57, range = 27–75) were divided into two groups, group A (n = 9) and group B (n = 6), due to different image acquisition protocols (details provided in the next section). All patients underwent image-guided biopsies following research MRIs, biopsy results were used as the ground truth, except for 2 lesions that were determined to be benign with follow-up imaging. In total, 13 distinct malignant and 11 benign lesions were identified. The malignant lesions included one invasive lobular carcinoma (ILC), six invasive ductal carcinoma (IDC), and three ductal carcinoma *in situ* (DCIS). The benign imaging findings included radial scar, phyllodes tumor, cystic papillary apocrine metaplasia, fibroadenomas, papilloma, and atypical ductal hyperplasia. Note that all patients included in the study were evaluated as high probability for malignancy by clinical assessment (i.e. BI-RADS 4-suspicious or 5-highly suggestive of malignancy; see Table 1), indicating inherent difficulty in discriminating malignant from benign lesions on clinical assessment.

Magnetic resonance imaging

Images were acquired on a Philips Achieva 3T-TX (Best, Netherlands) with a 16-channel bilateral breast coil and a 3D spoiled gradient recalled echo protocol. For group A, two types of dynamic data were acquired: fat-suppressed ultrafast DCE-MRI with temporal resolutions between 3.4 and 4.1 s, spatial resolution of $1.5 \times 1.5 \times 4 \text{ mm}^3$ with a SENSE factor of four in the right-left direction and two in the foot-head direction, and partial Fourier factor of 0.7 (in both k_y and k_z), and fat-suppressed high spatial resolution scans, with a temporal resolution of 55 to 63 s and a spatial resolution of $0.8 \times 0.8 \times 1.6 \text{ mm}^3$, SENSE of 2.5 in right-left direction and partial Fourier of 0.85 in k_y . The order of acquisition before the injection of 0.1 mM/kg MultiHance (Bracco, Milan, Italy) at 2 mL/s, was one pre-contrast high spatial resolution scan and then five pre-contrast ultrafast scans. The post-contrast acquisition consisted of 19 ultrafast scans and then four post-contrast high spatial resolution scans (see Table 2 for details on MRI scan parameters). We note that the descriptor “fast” was first associated with post-contrast subtracted images in abbreviated MR protocols as suggested by Kuhl et al. (28), which are acquired at temporal resolutions ranging from 60s to 120s. To avoid confusion with these protocols the term ‘ultrafast’ has been used for any

protocols that have temporal resolutions higher than those used in routine clinical protocols (24–25, 28–30).

For group B, three types of dynamic data were acquired: fat suppressed ultrafast DCEMRI with temporal resolutions between 1.7 and 3.5 s, spatial resolution of $1.5 \times 1.5 \times 4 \text{ mm}^3$, fast DCE-MRI with temporal resolutions between 6.2 and 7 s, spatial resolution of $1.5 \times 1.5 \times 3 \text{ mm}^3$, and high spatial resolution DCE-MRI with a temporal resolution of 55 to 63 s and spatial resolution of $0.8 \times 0.8 \times 1.6 \text{ mm}^3$. The order of acquisition before the delivery of contrast agent was one pre-contrast high spatial resolution scan, five pre-contrast fast scans, and then five pre-contrast ultrafast scans. The post-contrast acquisition consisted of 21–25 ultrafast scans, six post-contrast fast scans, and four post-contrast high spatial resolution scans. Contrast agent and other acquisition parameters were identical to those for group A.

For all the 15 patients studied, pre-contrast T_1 -weighted images were acquired with multiple flip angles (5, 10, 15, and 20 degrees for 12 patients; 5 and 15 degrees for three patients within group A), so that pre-contrast T_1 maps could be calculated.

Regards to post-processing, the non-rigid demons registration (31) was applied on DCEMRI datasets to minimize any patient motion that may occur during the acquisition (see Supporting Information and Figure S1, S2 for details on the registration technique). The reader is encouraged to consult Figure 1 as the outline of processes applied.

Tumor Segmentation

The lesions were segmented from the surrounding breast tissue on the registered high spatial resolution DCE-MRI data using a fuzzy c-means-based (FCM) method developed by Giger *et al.* (32). Details of lesion segmentation are provided in the Supporting Information.

Image Enhancement

Before vessel segmentation, a local-statistics-based intensity transfer function (33) was applied on the subtraction of the pre- from the post-contrast, high spatial resolution images for histogram normalization and enhancement. For each slice, an S-shaped transfer function given by [Eq. 6] was applied so that foreground enhancement as well as background suppression could be achieved simultaneously,

$$I_{enh} = \begin{cases} I_c - \sqrt{I_c^2 - I_{orig}^2}, & 0 < X \leq X_c \\ I_c + \sqrt{(I_{max} - I_c)^2 - (I_{max} - I_{orig})^2}, & X_c < X \leq X_{max} \end{cases}, \quad [6]$$

where I_{org} , I_{max} , and I_{enh} are the original subtraction image, maximal intensity in the original image, the enhanced image, respectively, and I_c is the inflection point of the S-shaped transfer function, set to be the 95th percentile of the intensity histogram (see Figure 2a and 2b for example).

Multiscale Hessian matrix based vessel segmentation and post-processing

Segmentation of the vasculature from the surrounding tissue was performed on the enhanced, high-resolution, subtraction images. A multi-scale Hessian-based filter (34–37) was first applied to generate a map of “vesselness”, which represents the probability for each voxel to contain a vessel. For an image, I , the Hessian matrix describes the second-order derivatives of intensity around each point in I (Eq. [7]),

$$H = \begin{pmatrix} \frac{\partial^2 I}{\partial x^2} & \frac{\partial^2 I}{\partial x \partial y} & \frac{\partial^2 I}{\partial x \partial z} \\ \frac{\partial^2 I}{\partial y \partial x} & \frac{\partial^2 I}{\partial y^2} & \frac{\partial^2 I}{\partial y \partial z} \\ \frac{\partial^2 I}{\partial z \partial x} & \frac{\partial^2 I}{\partial z \partial y} & \frac{\partial^2 I}{\partial z^2} \end{pmatrix}, \quad [7]$$

where x , y , and z are the canonical Cartesian axes. If we set the eigenvalues of the Hessian matrix to be sorted as $|\lambda_1| \geq |\lambda_2| \geq |\lambda_3|$, the Hessian-based vascular filter is given by [Eq. 8],

$$f(\sigma) = \begin{cases} 0, & \text{if } \lambda_2 > 0 \text{ or } \lambda_3 > 0 \\ \left(1 - e^{-\frac{R_A^2}{2\alpha^2}}\right) \cdot e^{-\frac{R_B^2}{2\beta^2}} \cdot \left(1 - e^{-\frac{S^2}{2\gamma^2}}\right), & \text{otherwise} \end{cases}, \quad [8]$$

Where $R_A = \frac{|\lambda_2|}{|\lambda_3|}$ differentiates vessels from sheet-like structures, $R_B = \frac{|\lambda_1|}{\sqrt{|\lambda_2\lambda_3|}}$ differentiates

vessels from spherical structures (see Figure 2c for the relationship between local structure and eigenvalues of Hessian matrix), $S = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}$ suppresses noise structures, and $\sigma = r\sqrt{2}$ specifies the diameter of the vessels to be detected, where r is the vessel radius. The scale parameters α , β , and γ are used to balance tube-sheet differentiation, tube-sphere differentiation, and noise structures suppression, respectively. The larger the value of the parameter, the smaller effect the corresponding criterion will provide. With no prior information about surrounding background structure, differentiation for sheet-like and blob-like structures are usually considered of similar importance so that $\alpha \approx \beta$. Additionally, to avoid blurring the image the strength of noise structure suppression is usually set to be weaker than that of structure differentiation; i.e., $\alpha, \beta \ll \gamma$. In our processing, α, β, γ were empirically set to 0.25, 0.25, and 10 (34), respectively. Considering the range of radii observed for the breast vasculature, the filter was calculated with σ ranging from 0.20 to 1.00 with a step of 0.20. The maximum filter output across all scales was ultimately assigned as the vesselness for each voxel (32). This strategy was able to capture both large and small vessels (see Figure 2e for an illustration of a ‘vesselness’ map.)

After generating the vesselness map, a threshold was set to segment the vasculature from the background. To automatically determine this threshold, the filter in [Eq. 8] was applied on a region of a fixed size ($50 \times 100 \text{ mm}^2$ in transverse plane) covering the internal thoracic vessels, and the 98.5% percentile of the “vesselness” histogram of this region served as the threshold to extract vessel-like structures (38). To fill holes and small gaps in the resulting binary map, directional dilation was performed on the non-vascular voxels near the detected vessel segments (37). The resulting segmented vessels were then skeletonized (i.e., thinning to their centerlines) and converted to a graph, where edges of the graph were individual vessel segments, and nodes were branching points or isolated end-points. Ultimately, a 3D reconstruction of breast vasculature was generated (see Figure 2f for an illustration of vessel segmentation and graph analysis).

Vessel Tracking/Detection

Based on the 3D reconstruction of vasculature, the “tumor-associated vessels” (i.e., those vessels physically connected to the tumor) can be identified. During this process, two situations were encountered: 1) the vessels directly “touch” the tumor in the sense that a voxel within a segmented vessel is physically adjacent to a voxel associated with the segmented tumor, and 2) vessels separating into multiple small branches near the tumor, but these connections are not detectable by the segmentation scheme outlined in the previous section. While the first condition requires no further analysis, for the latter condition the goal is to estimate the existence of a tumor-vessel connection.

We considered three reasons which may cause a missing connection between a vessel and the tumor itself. First, the vessel segments are simply too small to form visible, tube-like structures given the spatial resolution, causing them to be undetectable with the Hessian-based filter. However, though below the resolution of the acquisition, these smaller vessels should still yield some degree of local enhancement. Thus, the original subtraction image could provide information for connection estimation (see Figure 2d for illustration). Second, the small branches can form locally tube-like structure, which means the corresponding regions have a higher vesselness value than surrounding tissue. But, due to the partial volume effect, the vesselness value is not sufficient to avoid being ignored by the thresholding step. Thus, the whole vesselness map could contain additional information for identifying these small vessels (see Figure 2e for illustration). Moreover, the connections could simply be absent because of limited signal-to-noise, so that intensity-related features cannot recover the missing information. For this situation, we adapted the tensor voting method (39) to estimate the direction of most likely extension of the end of the vessel segments (see the Supporting Information and Figure S3 for details on tensor voting method). This method generated a saliency map where high values represent high probability for continuity of segments (see Figure 2g for illustration). We defined a cost map formed as a linear combination of these three measures (i.e., the subtraction, vesselness, and tensor voting maps) as defined by [Eq. 9]. The combination was then converted to a cost-map ranging from 0 to 1 with the exponential function in [Eq. 10],

$$Costmap = e^{-\alpha I}, \quad [9]$$

$$I = \phi_s \cdot (\text{subtraction}) + \phi_v \cdot (\text{vesselness}) + \phi_t \cdot (\text{tensor voting map}), \quad [10]$$

where the ϕ_i correspond to the weight of the i^{th} measure, $\alpha > 0$, and $\phi_s + \phi_v + \phi_t = 1$. For simplification, we set $\alpha = 10$, $\phi_s = \phi_v = \phi_t = 33.3\%$. Thus, in the cost map, the lower the value of one voxel, the higher probability for unsegmented small vascular branches to exist at the specific voxel's location (see Figure 2h for an illustration of cost map).

For each individual vessel segment that terminated within 10 mm of the tumor edge, [Eq. 9] was used to compute the lowest-cost path from the termination of this vessel segment to all other vessels as well as the edge of lesion *via* the Dijkstra's algorithm (40). If the lowest cost led to a lesion, the vessel would be identified as a "tumor-associated vessel". This strategy eventually allows for the detection of vessel segments that have a high probability of contacting the lesion, as well as the path that is the most likely physical connection between the vessel and tumor (see Figure 2i for illustration).

After applying the tracking algorithm, all vessels were labeled based on their relationship with the lesion as either 1) directly touching the tumor (labeled as "1"), 2) spreading towards the tumor as determined by the algorithm just described (labeled as "2"), and 3) no connection to the lesion (labeled as "0"). The vessels associated with each lesion were then automatically counted by going through all individual vessels and recording the number of vessels with non-zero labels.

Pharmacokinetic modeling

With the computed pre-contrast T_1 map, the dynamic signal intensity time course can be calibrated to the time course of concentration of contrast agent, thereby enabling pharmacokinetic analysis (see ref. (1) for details). As the ultrafast DCE-MRI protocol recorded data for approximately 1 min after the injection of contrast agent, only the initial uptake and plateauing of the curve was captured, thereby precluding an accurate estimate for the extravascular extracellular volume fraction (i.e., v_e). Thus, for pharmacokinetic analysis, we chose a simplified version of the standard Tofts-Kety model (1) which assumes that the exchange of contrast agent between the two components is unidirectional (i.e., only from the plasma to the interstitial space) with the rate K^{trans} :

$$C_t(T) = K^{\text{trans}} \int_0^T C_p(t) dt + v_p C_p(T), \quad [11]$$

where $C_t(t)$ and $C_p(T)$ are the time courses of the concentration of contrast agent in the tissue and the plasma (the so-called arterial input function, or AIF), respectively.

Typically, the AIF is obtained from large arteries visible in the imaging field-of-view. If this $C_p(t)$ is placed directly in [Eq. 11], errors in the estimated parameters could occur due to delay or dispersion of $C_p(t)$ by the time it arrives at the voxel of interest. This can be

exacerbated in ultrafast DCE data. Thus, we incorporated a delay term in $C_p(t)$. First, for each patient, the individual $C_p(t)$ was estimated from the signal intensity time course of the internal thoracic arteries (shown in Figure 3a) which were semi-automatically identified using a previously established method (please see (41) and the Supporting Information and Figure S4 for details on individual AIF determination). The individual AIFs were then aligned and averaged to form a population AIF (see Figure S5), $C_{p, pop}(t)$. When applying to each voxel in a particular patient, the population AIF was shifted by an amount equal to the difference between the arrival time at the voxel and the enhancement time of the population AIF, $delay_{pop}$; this procedure allows for temporally aligning the $C_p(t)$ and $C_A(t)$ curves (see Figure 3c and the Supporting Information for more details). That is, for each voxel, the $C_p(t)$ term in [Eq. 11] was replaced with that given in [Eq. 12]:

$$C_p(t) = \begin{cases} 0, & 0 < t \leq delay_{pop} \\ C_{p, pop}(t - delay_{pop}), & t > delay_{pop} \end{cases}. \quad [12]$$

Vascular measures

After the vascular tree for the whole breast was determined, we calculated the number of vessels associated with each lesion (termed *count*). Additionally, we computed the ratio of the actual length to the linear distance between endpoints of a vascular segment for each vessel (42; and termed this the distance metric, *DM*), which measures the tortuosity. Thus, for each lesion, two morphological and three functional metrics were quantified: *count*, *DM*, K^{trans} , v_p and the *delay* (which refers to the delay of bolus arrival time at each voxel location compared to the initial enhancement time of the individual AIF as measured at the internal thoracic arteries of the patient).

The vasculature was color-coded according to the bolus arrival-time estimate to establish the temporal and spatial relationship between input and output vessels. With the tumor-associated vessels and the bolus arrival-time estimates, the lesion input and output functions (LIF and LOF, respectively) were generated. For each lesion, we defined “vascular voxels” to be the voxels within identified tumor-associated vessels that are significantly enhanced. Vascular voxels with the lowest 5% arrival-time were then defined as “lesion input regions”, and voxels with the highest 5% arrival-time as “lesion output regions”. Finally, the estimate of LIF or LOF for each lesion were obtained by averaging the signal intensity time-courses of “lesion input regions” or “lesion output regions”.

Statistical Analysis

The nonparametric Wilcoxon rank sum test was used to assess differences in both the morphological and functional measures between malignant and benign lesions. Univariable and multivariable logistic regression modeling was also used to assess their ability to differentiate malignant from benign lesions. Model performance was evaluated by receiver operating characteristic (ROC) curve analysis with leave-one-out cross-validation. Areas under the ROC curves (AUCs), as well as sensitivity and specificity at the optimal cutoff point as determined by the maximum Youden’s index, were calculated for comparison.

Additionally, Spearman's correlations were calculated to determine the statistical relationship between the measures. Statistical significance was defined as $P < 0.05$.

Results

Patient summary statistics

In total, 15 patients presenting with a total of 24 lesions were included in the analysis; 13/24 (54%) were malignant and 11/24 (46%) were benign (Table 1). No significant difference in lesion size was found between malignant and benign lesions ($p = 0.202$). All the patients were reported to be suspicious or highly suggestive of malignancy based on clinical assessment (BIRADS = 4 or 5), though 5/15 patients had only benign lesion(s). Figure 3d shows the results of pharmacokinetic modeling for representative malignant (top row) and benign lesions (bottom). The first column of panel (d) shows the [Eq. 12] fitting in one example voxel from each patient, where the red stars are measured using the ultrafast DCE-MRI acquisition (SI/S_0 refers to signal intensity normalized by S_0 , the relaxed signal for a 90° pulse when $TR \gg T_1$), and the blue curves are the model fits. The other columns present the K^{trans} , v_p , and bolus arrival time maps, respectively, of the central slice of the lesion, overlapped on the subtraction of the same slice. In particular, the patient shown in first row presented $K^{trans} = 0.12 \pm 0.0039 \text{ min}^{-1}$ (mean $\pm$ 95% CI), $v_p = 0.050 \pm 0.0011$ (mean $\pm$ 95% CI), delay = $10.0 \pm 0.02 \text{ s}$ (mean $\pm$ 95% CI); the patient shown in second row presented $K^{trans} = 0.18 \pm 0.0078 \text{ min}^{-1}$ (mean $\pm$ 95% CI), $v_p = 0.015 \pm 0.00035$ (mean $\pm$ 95% CI), delay = $10.1 \pm 0.02 \text{ s}$ (mean $\pm$ 95% CI).

Breast vasculature segmentation and tumor-associated vessel identification

Within the lesions that did have tumor associated vessels, 13 are malignant and nine are benign; there are also two lesions in which no tumor associated vessels were identified, and both are benign. Figure 4 presents the intermediate data types that are generated when building the vessel skeleton and selecting the tumor associated-vessels. In particular, the figure displays the vessel and lesion segmentations for two representative patients, as well as detection of the tumor-vessel connections. The left columns present a benign tumor, while the right column is malignant. Panels (a)–(b) present the maximum intensity projections (MIPs) of high spatial resolution subtraction images for two cases. Panels (c)–(d) show the MIPs of the segmented breast vasculature, where the grey scale refers to the vesselness value and ranges from 0 to 0.4. Panels (e)–(f), display the 3D reconstruction of both segmented vessels (green tubes) and lesions (red volumes) with orientation labeled on axes. Finally, the bottom row presents the 3D reconstruction of the skeleton of segmented vascular tree (black curves) and lesion (grey volume), where the identified tumor-associated vessels are covered by red stars and the most possible vessel-tumor connection paths are shown as blue dots. The counts of tumor-associated vessels for the two cases were 5 and 16 (from left to right), respectively. Of particular note, is the patient in the right column. When considering the MIP of Figure 4b, there appears to be three large vessel segments touching the lesion. However, after vessel segmentation in 3D, it is clear that these vessels are connected to each other and not the tumor itself (Figure 4d), thereby stressing the importance of studying vascular structures in 3D.

Bolus arrival time visualization in breast vasculature

Using the estimated arrival-time maps (estimated using [Eq. 11]), the temporal order for the bolus of contrast agent travelling through the vasculature can be visualized by color-coding. Figure 5 shows the visualization in three representative cases, where the arrival time value was normalized to the initial time of enhancement of the internal thoracic artery for each patient (the location of the internal thoracic artery is indicated in Figure 3a). In particular, the arrival times at vessel regions for the three patients are respectively 11.0 ± 0.1 s, 9.2 ± 0.1 s, 7.3 ± 0.1 s (mean $\pm$ 95% CI). The color-coded 3D reconstruction of vasculature helps to distinguish the arteries and veins. As shown in each panel of Figure 5, hot color represents an early bolus arrival-time, which means the corresponded vessels are likely to be arteries; cold color represents a late arrival-time, suggesting the corresponded vessels to be veins.

Lesion input and output functions assessment

Of the 13 malignant lesions, valid lesion input and output functions could be identified in 11 cases. Among the 11 benign lesions, four had valid lesion input and output functions. Reasons for not obtaining a valid LIF or LOF included 1) there were no tumor-associated vessels identified, or 2) the voxels within the identified tumor-associated vessels were not significantly enhanced to provide an input or output function. The latter situation could be due to the limits of signal-to-noise ratio, or the partial volume effect.

The averages of the lesion input and output functions for malignant and benign lesions are compared (shown in Supporting Figure S6). Although the statistical significance is limited, the LIFs and LOFs tend to show differences ($P = 0.16$) between benign and malignant lesions. More discussion on this analysis can be found in Supporting Information.

Assessments of morphological and functional measures

As shown in Figure 6 and summarized in Table 3, *count*, K^{trans} , and v_p had significant differences between malignant and benign lesions based on the Wilcoxon test ($P = 0.009$, 0.034 and 0.010 , respectively). *DM* and *delay* showed no significant differences between malignant and benign lesions ($P = 0.12$ and 0.18). The diagnostic performances were compared for *count*, *DM*, K^{trans} , v_p , and *delay*, using ROC analysis of univariable logistic regression modeling and returned AUCs = 0.76 , 0.33 , 0.63 , 0.70 and 0.57 , respectively. Spearman's correlation between the measures are given in Supporting Table S1; only K^{trans} and v_p showed significant correlation ($P < 0.0001$).

Diagnostic performance of multivariate linear regression models

To determine if the ability to separate malignant from benign disease could be improved by combining the morphological and functional measures, several univariate and multivariate regression models were compared (see Table 4). First, only morphological metric(s) were used to generate models; in particular, we generated models using 1) *count* and *DM*, 2) *count* only, and 3) *DM* only. The regression model which incorporated only *count* yielded the best performance with an AUC = 0.76 . Second, only functional metric(s) were used to generate models; in particular, 1) K^{trans} , v_p , and *delay*, 2) K^{trans} and v_p , 3) K^{trans} and *delay*, 4) v_p and *delay*, 5) K^{trans} , 6) v_p , and 7) *delay*. The regression model which included v_p and

delay yielded the best performance with an AUC = 0.79. Finally, both morphological and functional measures were used to generate models, which included all possible combinations of the five measures. The regression model that included *count* and *delay* yielded the best performance of AUC = 0.91. The model including all parameters (i.e., *count*, *DM*, K^{trans} , v_p , *delay*) did not perform well due to overfitting.

Discussion

We have proposed an image processing framework that can automatically detect tumor-associated vessels and identify the vascular inputs and outputs of lesions. This methodology aimed to extract both morphological and functional information about lesion blood supply condition by combining ultrafast DCE-MRI scans with standard high spatial resolution DCE scans. With this methodology, we generated 1) morphological vascular metrics representing the number and tortuosity of vessels associated with individual breast lesions (*count* and *DM*), 2) functional metrics representing lesion vascular input and output kinetics (LIF and LOF), and pharmacokinetic parameters, K^{trans} , v_p and *delay*, representing characteristics of microvasculature within the lesion. The metrics *count*, *DM*, K^{trans} , v_p and *delay* were assessed for the accuracy of malignant discrimination, individually and in linear combinations. The statistical assessments indicated that *count*, K^{trans} , and v_p showed significant differences between malignant and benign lesions, and that K^{trans} and v_p were significantly correlated. The best multivariate models for differentiation included unique parameters from our automated framework, *count* and *delay*. These results suggested that integrating quantitative analysis of both morphological and functional measures could improve the diagnostic ability of breast MRI. Furthermore, the vascular inputs and outputs tended to show differences between malignant and benign lesions, suggesting there may be characteristic microcirculation patterns of malignancy that are observable on breast MRI.

The potential for using vessel analysis for malignancy detection has been suggested by many previous studies. In 2001, Mahfouz *et al.* (10) assessed the association between breast cancer and higher vascularity by visually assessing whether vascularity was higher on the ipsilateral breast, contralateral breast, or equal on both sides using MIPs. Using this procedure, the investigators achieved a sensitivity of 76.5%, a specificity of 57%, and an accuracy of 72.6%. Several follow ups studies obtained similar results speaking to the potential diagnostic utility of vascular features of the breast (11–15). Follow-up studies focused on characterizing both whole-breast vascularity as well as vessels near the lesion (17–19). For example, Malich *et al.* (17) identified vessel adjacent to suspicious lesions on subtraction images and found 63% of 268 malignant lesions had such vascular structures, versus only 28% of 60 benign lesions. More recently, studies have attempted to automatically detect vessels in breast DCE-MRI. Vignati *et al.* (35,36) designed an algorithm for automatic whole-breast vascular mapping on DCE-MRI data, based on a multiscale 3D Hessian matrix analysis, and significant differences were found in vascular volume and the number of vessels before or after neoadjuvant chemotherapy (36). Petrillo *et al.* (43) reported a semi-automatic method, performed on MIPs of subtraction images, for detecting the vascular map and primary feeding vessel of the breast harboring the lesion. An excellent reliability for semi-automatic assessment, as well as agreement with radiologic consensus was found to identify the origin of the feeding vessels.

Our present study seeks to extend the results outlined in the previous paragraph by developing automated tumor-associated vessel detection and quantification methods, and combining it with functional analyses, taking advantage of ultrafast sampling. The result that only K^{trans} and v_p were significantly correlated among all assessed measures, indicated that *delay*, *count*, and *DM* may contain information that is not characterized by K^{trans} and v_p . Thus, adding these novel measures has the potential to benefit clinical applications (e.g., diagnosis, assessment of aggressiveness of known cancers to aid in treatment planning). The assessment of the diagnostic performance further supports the hypothesis that coupling morphological and functional information related to tumor vasculature could enhance diagnostic accuracy beyond what can be achieved by either approach individually. Furthermore, the patients included in this dataset were all BI-RADS scores of 4 or 5. The above results suggest that the quantitative analysis extracting and integrating measures that are related to tumor vasculature could assist in diagnosis these difficult cases.

The current study has several limitations. For example, the size of the vessels that can be resolved is (of course) intimately connected to the spatial resolution and signal-to-noise of the images themselves. Since the breast vasculature was segmented on images with a voxel size of $(0.8 \text{ mm})^3$, vessels with radii much smaller than 0.8 mm cannot be directly segmented. We attempted to overcome this limitation by applying a cost-based search to track possible paths connecting segmented vessels and the lesions, but this estimate cannot be directly validated with our current dataset. Future work in controlled pre-clinical or phantom studies are needed for validation, in which the true vascular architecture can be known *a priori*. Another limitation of the study is that our vessel detection method used T_1 -weighted, fat-suppressed and contrast-enhanced subtraction MR images as inputs. Thus, it is currently limited in patients with marked background parenchymal enhancement (44). Additionally, the individual AIFs were extracted from the thoracic arteries, which are small compared to the 3×3 windows used to generate the average signal intensity time course. This measurement could be affected by partial volume and motion artifacts, which could lead to an AIF with an underestimated enhancement rate and/or peak height. Such a measurement error could result to estimates of K^{trans} and v_p that are larger than their true values. Finally, only 24 lesions (in 15 patients) were available for this study, and there were subtle differences in scan parameters amongst the patients. Future work is needed to validate the statistical results with a larger (and more homogeneous) patient cohort and more uniform acquisition protocol. Additionally, a larger data set would allow for investigating the relationships between characteristics of lesions (size, type, mass, non-mass, etc.) and the number of tumor associated vessels. For example, although the lesions included in this study are challenging in MRI-detection (BIRADS 4 or 5), they are large in size compared to typical MRI-detected false positive lesions. Thus, future studies are needed to explore the specificity of lesion differentiation with proposed method in the small MRI-detected lesions.

Conclusion

This study presented a novel framework for integrating vessel detection with quantitative analysis of ultrafast DCE-MRI data to yield a quantitative characterization of both morphological and functional features of tumor associated vasculature. Our preliminary results suggested that combining these data types have the potential to improve diagnostic

accuracy compared to standard measures, especially for the cases that are challenging using only clinical assessment. Moreover, the comparison of vascular inputs and outputs between malignant and benign lesions also suggested characteristic microvascular patterns of malignancy which should be further investigated. Analysis with larger sample size are needed to validate these preliminary results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flow chart describing all the operations applied to the data. Both ultrafast and high spatial resolution DCE images were registered for motion correction and used as inputs of downstream processing. Lesions were segmented using high spatial resolution DCE series with a FCM-based algorithm. Whole-breast vasculature segmentation was performed on the subtraction of pre-contrast high spatial images from first frame of post-contrast images. Tumor-associated vessels were identified via spatial overlapping or tracking. Additionally, the ultrafast DCE series were used for pharmacokinetic modeling to generate parametric maps of K^{trans} and v_p as well as bolus arrival time. The identified vessels and estimated parameters were then integrated to generate metrics representing morphological or functional feature of tumor microcirculation. Ultimately, statistical analyses were done to assess the diagnostic performance for these metrics to discriminate malignant or benign lesions.

Figure 2.

Illustration of vessel segmentation and tumor-associated vessel detection. Panel (a) indicates the intensity histogram for one slice of one patient's subtraction image. Panel (b) shows the intensity transfer function ([Eq. 6]) for this slice, where the inflection point is given by the value obtained by the 95th percentile from panel (a). The three types of local structure and the corresponding features of the Hessian matrix eigenvalues are shown in panel (c) (45). The conceptual 2D illustration of vessel segmentation is displayed in panels (d) input image, (e) vesselness map, and (f) segmented vessels and graph analysis. The bottom row of panels illustrates tumor-associated vessel detection process *via* through the tensor-voting (g) and cost-map (h), which yield the identified tumor-associated vessels.

Figure 3.

Bolus arrival-time estimate and pharmacokinetic modeling. Panel (a) displays the internal thoracic arteries on a transverse, post-contrast slice (about 15 s after contrast agent injection) in one patient. A half-logistic function ([Eq. 11]) is fit to the time course to estimate the bolus arrival-time (panel b). The population AIF is then aligned using the delay of the estimated arrival-time for each voxel compared to the enhancement time of the population AIF (panel c). Panels (d) show the results of pharmacokinetic modeling, with each row presenting one representative patient. From left to right, columns show model fitting in an example voxel and the corresponding parametric maps, K^{trans} , v_p , arrival-time.

Figure 4.

Segmentation and tumor-associated vessel identification results for two representative patient cases (left column: benign phyllodes tumor, right column: IDC). Panels (a) - (b) present the maximum intensity projection (MIP) of the whole breast subtraction images. After enhancing by the S-shaped intensity transformation and applying the Hessian-based filter, the images are then segmented and each voxel is assigned “vesselness” value as in panels (c) - (d) which can then be rendered in 3D in the same image space as the segmented lesions of panels (e) - (f). The final row of images depicts the 3D reconstruction of the vessel

tree and the identified tumor-associated vessels. Note the red arrows show vessels that could be mistakenly identified as tumor-associated vessels if only using the MIP.

Figure 5. Color-coded breast vasculature indicating the arrival time for three representative malignant (panels a and b) and benign (panel c) lesions. Arrival time = 0 refers to the initial time of enhancement at the internal thoracic arteries for each patient.

Figure 6.

Wilcoxon rank sum test of the quantitative measures. Panels (a) - (e) depict the count of tumor-associated vessels, median of distance metric (DM) of tumor-associated vessels, median of K^{trans} , median of v_p , and the median of arrival-time, respectively, between malignant and benign tumors.

Table 1

Patients and lesions characteristics (15 patients, 24 lesions)

Characteristic	N (%) or median (range)
Patient age (year)	57 (27 to 75)
Lesion size (mm)	24 (5 to 111)
Histopathology	
Benign	11 (46%)
Malignant (DCIS ^a , invasive)	13 (54%)
Lesion type	
Mass	13 (54%)
Nonmass	11 (46%)
Detectable by	
Palpation	1 (4%)
Ultrasound	18 (90%) (4 did not undergo US)
Mammography	18 (75%)
Clinical assessment	
4-Suspicious	10 (67%)
5-Highly suggestive of malignancy	5 (33%)

^aDuctal carcinoma *in situ*

Table 2

MRI scan parameters

MRI parameters	T_1 -mapping	Ultrafast DCE-MRI	Fast DCE-MRI	High spatial resolution DCE-MRI
Scan sequence	Spoiled GRE ^a	Spoiled GRE	Spoiled GRE	Spoiled GRE
Time (s)	80/160	Group A: 90 Group B: 42	80	340
Repetition time (ms)	10	3.2	3.2	5.0
Echo time (ms)	2.4	1.6	1.6	2.5
Flip angle(s) (deg)	5,10,15,20	10	10	10
Acquisition matrix	340 × 340	228 × 154	228 × 228	425 × 425
Slice thickness (mm)	1.6	4	3	1.6
Slice spacing (mm)	0.8	2	1.5	0.8
Temporal resolution (s)	40	Group A: 3.4 to 4.1 Group B: 1.7 to 3.5	6.2 to 7.1	65

^aGradient recalled echo sequence

Table 3

Measurements of benign and malignant breast lesions (n = 24)

Metrics	Benign (n = 11) Median (range)	Malignant (n = 13) Median (range)	P-value (Wilcoxon)	AUC ^a (LOOCV ^b)
Morphological vascular metrics				
<i>count</i>	3 (0 to 8)	8 (1 to 25)	0.009	0.76
<i>DM^c</i>	1.3 (1.2 to 1.6)	1.2 (1.1 to 1.5)	0.12	0.33
Functional metrics				
<i>K^{trans}</i>	0.013 (0.0026 to 0.17)	0.073 (0.013 to 0.14)	0.034	0.63
<i>v_p</i>	0.0022 (0.00025 to 0.017)	0.021 (0.0020 to 0.099)	0.010	0.70
<i>delay</i> (s)	10.5 (6.4 to 22.4)	8.9 (2.8 to 13.1)	0.18	0.57

^aArea under curve^bLeave-one-out cross validation^cDistance metric

Table 4

Diagnostic performance of multivariate logistic regression models

Models	LOOCV ^a		AUC ^b
	sensitivity	specificity	
With morphological metric(s)			
Complete — (<i>count</i> , DM^c)	0.69	0.91	0.56
Best performance — (<i>count</i>)	0.77	0.91	0.76
With functional metric(s)			
Complete / Best performance — (K^{trans} , v_p , <i>delay</i>)	0.54	1.00	0.78
Best performance — (v_p , <i>delay</i>)	0.69	0.91	0.79
With both morphological and functional metric(s)			
Complete — (<i>count</i> , DM , K^{trans} , v_p , <i>delay</i>)	0.69	1.00	0.69
Best performance — (<i>count</i> , <i>delay</i>)	0.77	1.00	0.91

^aLeave-one-out cross validation^bArea under curve^cDistance metric