Accurately Differentiating Benign from Malignant Contrast-Enhancing Breast Lesions Using An Automated Method of Quantitative Washout Kinetics and Fractional Lesion Volume Analysis

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Introduction: Dynamic contrast-enhancing (DCE) breast MRI has been shown to be very sensitive in cancer detection [1, 2]. Most malignant tumors demonstrate a rapid initial enhancement followed by a wash-out (WO) or plateau curve in the post-contrast signal intensity time courses, whereas most benign lesions exhibit a slower but persistent enhancement without the WO behavior [1]. However, false-positive kinetic curves were frequently observed in many benign lesions including fibroadenomas, proliferative fibrocystic changes, atypical ductal hyperplasia, etc., resulting in a low specificity and consequently a smaller positive predictive value (PPV) for biopsies [3, 4]. The WO curve mainly reflects the hypervascularity associated with tumor angiogenesis [5, 6], and the total volume of the WO voxels showing the WO behavior may account for the degree of the hypervascularity of the tumor. Accordingly, the WO volume fraction relative to the whole lesion volume has the potential to be a biomarker for indicating the degree of hypervascularity associated with tumor angiogenesis. Benign proliferative breast diseases can also produce the WO curve, yielding an overlap between benign and malignant lesions and making them hardly distinguishable. Nevertheless, the WO volume fraction for benign proliferation might be relatively small in comparison to that for tumor angiogenesis, considering that an aggressive cancer cell growth is most likely accompanied by relatively larger angiogenesis. Thus, measuring the WO volume fraction may help in differentiating benign from malignant contrast-enhancing lesions. In this study we investigated using the WO volume fraction as a new biomarker for differentiating benign from malignant contrast-enhancing breast lesions, aiming to improve the positive predictive value of biopsies and consequently to reduce the number of unnecessary biopsies.

Methods and Materials: Fifteen patients (age from 34 to 63 years) with breast lesions $\geq$7 mm underwent a standard clinical breast MRI exam. Sixteen breast lesions were included that met the criteria: (1) a lesion was radiologically reported as suspicious for malignancy; and (2) its pathology report was available for comparison. The exam was acquired on a GE clinical 1.5T scanner using a dedicated 8-channel breast coil with ASSET technique, and included a DCE FSPGR 3D scan (FOV 32 cm, flip angle 10°, matrix 320×320, slice thickness 2 mm, slab location 116, and ZIP2). An intravenous line was established before imaging for later delivery of gadobenate dimeglumine (Gd-BOPTA) contrast agent (0.2 mL/kg), and the contrast agent was injected at a rate of 3cc/s over 7-10 seconds followed by a 20-cc saline solution flush. One set of pre-contrast images was acquired immediately prior to the administration of the contrast agent. The contrast agent injection and the MR dynamic imaging acquisition were synchronized, and the first post-contrast phase was initiated after a 30s scan delay. Post-contrast imaging included five phases with a scan time of 90s for each phase. In-house software designed to automatically detect the boundary of manually selected contrast-enhanced lesions was used to delineate the lesion and its bordering tissue (Fig. 1A). A region of interest (ROI) of the bordering tissue was established to have the same total area as the lesion. A second adjacent tissue ROI with the same total area size was also generated outside the bordering tissue ROI as shown in Fig. 1(A). A linear least squares fitting of the post-contrast signal intensity time course was performed and then the slope of the fitted line was computed pixel-by-pixel; a negative slope indicated a WO curve (Fig. 1B). The total volume for a lesion and the total volume of WO voxels within the lesion were computed, and the ratio of the latter to the former was further calculated to yield the WO volume fraction for the lesion.

Results and Discussion: We first tested the reliability of our method for the lesion determination. The signal intensity of the first post-contrast image was compared between the lesions and their surrounding tissues. The signal intensity was 1582±334 (mean±SD) for the lesions, 673±161 for the bordering tissue ROI, and 583±142 for the adjacent tissue ROI, respectively. The signal intensity of the lesions was significantly larger than that of the surrounding tissues (t-test, $p<10^{-7}$), but, as expected, no significant difference was observed between the bordering tissue ROI and the adjacent tissue ROI ($p>0.10$), showing the reliability of our method for determining the lesion boundary. The method objectively defined contrast-enhanced lesions from surrounding tissues. We then investigated using the WO volume fraction as a biomarker for differentiating benign from malignant contrast-enhancing breast lesions. All breast lesions were grouped as either benign (1 fibroadenoma and 4 fibrocystic changes) or malignant (11 infiltrating ductal carcinomas) according to pathology reports. (Note that all these lesions were radiologically reported as highly suspicious for malignancy, and subsequently core biopsies were performed.) For the benign lesions (BL), the mean and standard deviation of the WO volume fraction was 8.4±5.7 (%), ranged from 2.4% to 17.3%. For the malignant tumors (MT), however, the WO volume fraction was 45.8±19.7 (%) with the range from 22.1% to 86.9%, significantly larger than that for the BL ($p<0.0001$) (Fig. 2). This significantly larger WO volume fraction for the MT was most likely produced by the hypervascularity associated with tumor angiogenesis, but the smaller WO volume fraction for the BL mainly reflected a relatively small amount of increased vascularity associated with benign proliferative breast diseases and fibroadenoma. Fig. 3 shows a scatter plot of WO volume fraction versus lesion volume, demonstrating the separated distribution for the MT and the BL. These results can be used to characterize contrast-enhancing breast lesions. If we choose 20% as the volume fraction threshold for characterizing these lesions, i.e., a volume fraction larger than the threshold would be characterized as malignant and a volume fraction smaller than the threshold would be characterized as benign, respectively, then all of the MT would be identified as malignant and all of the BL as benign, improving the PPV of biopsies to 100%. In conclusion, the WO volume fraction of a contrast-enhanced lesion was significantly different between the BL and the MT, providing a sensitive biomarker for differentiating benign from malignant contrast-enhancing breast lesions. Using this WO volume fraction as a predictor, it could significantly improve the PPV and consequently significantly reduce the number of unnecessary biopsies.
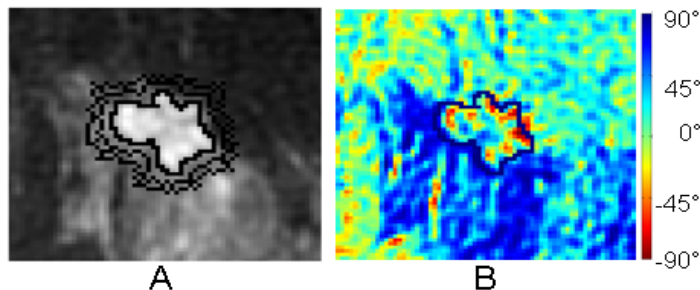

Fig. 1 A: Illustration of a lesion, a bordering tissue ROI, and an adjacent tissue ROI, respectively, based on the first post-contrast image.
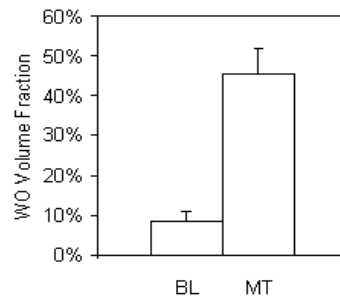B: Corresponding image of the degree of slope for the DCE period.

Fig. 2 Comparison of WO volume fraction between the MT and the BL. The error bar denotes the standard error of the mean.
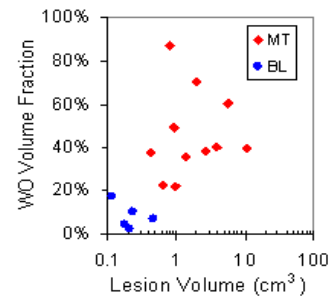
Fig. 3 Distribution of WO volume fraction versus lesion volume.

References: 1. Kuhl, CK, *et al*, Radiology 211: 101-110, 1999. 2. Bluemke, DA, *et al*, JAMA 292: 2735-2742, 2004. 3. Orel, SG, *et al*, Radiology 190: 485-493, 1994. 4. Orel, SG, Radiology 211: 5-7, 1999. 5. Buadu, LD, *et al*, Radiology 200: 639-649, 1996. 6. Su, MY, *et al*, JMRI, 18: 467-477, 2003.