Validating lesion washout volume fraction as a biomarker for improving suspicious breast lesion characterization

Jie Huang[1], Sarah Schafer[1], Lori Hoisington[1], and Gerald Aben[1]
[1]*Department of Radiology, Michigan State University, East Lansing, MI, United States*

Introduction: Dynamic contrast-enhanced (DCE) breast MRI has been shown to be very sensitive in cancer detection [1,2]. Most malignant tumors demonstrate an initial enhancement followed by a rapid wash-out (WO) or plateau curve in the post-contrast signal intensity time courses. The WO curve mainly reflects the hypervascularity associated with tumor angiogenesis essential for tumor growth [3-5]. Although most benign lesions exhibit a slower but persistent enhancement without the WO behavior [1], false-positive kinetic curves were frequently observed in many benign lesions including fibroadenomas, proliferative fibrocystic changes, etc. [6,7]. This results in a low specificity and consequently many unnecessary biopsies. Our recent preliminary study with a sample consisting of 28 contrast-enhanced lesions demonstrates the potential of using WO volume fraction as a new biomarker for differentiating benign from malignant contrast-enhancing breast lesions [8]. The hypothesis is that WO volume fraction, those voxels showing rapid wash-in and wash-out behavior in proportion to total lesion voxels showing rapid wash-in, has the potential to be a biomarker for indicating the degree of hypervascularity associated with tumor angiogenesis. Currently, the usual clinical approach is based on selecting only the most suspicious voxels within a lesion to characterize that lesion and does not incorporate the proportion of the most suspicious wash-out voxels to the total lesion volume. We hypothesized that the WO volume fraction for benign proliferation would be relatively small in comparison to malignant lesions, considering that an aggressive cancer cell growth is most likely accompanied by relatively larger angiogenesis [8]. In this study, with a sample consisting of 94 contrast-enhanced lesions, we further tested this hypothesis and the WO volume fraction as a biomarker for potentially improving the characterization of suspicious contrast-enhancing breast lesions.

Methods and Materials: Over 878 standard clinical breast MRI examinations since 2007 from our clinic were retrospectively reviewed. Study lesions were (1) mass like enhancement larger than 5 mm and (2) assigned a BI-RADS assessment of 4 (suspicious abnormality), 5 (highly suggestive of malignancy), or 6 (known biopsy-proven malignancy). The study excluded those lesions with BI-RADS assessment of 4 or 5 that did not go on to biopsy or their histopathology reports could not be obtained. A total of 94 contrast-enhanced lesions (39 lesions with BI-RADS assessment of 4, 9 lesions with BI-RADS assessment of 5, and 46 lesions with BI-RADS assessment of 6) in 87 patients comprised the lesion set for this study. The MRI examinations were acquired on a GE clinical 1.5T scanner using a standard clinical protocol for breast DCE-MRI [8]. Post-contrast imaging included five phases with a scan time of 90s for each phase. All lesions were identified by a board-certified experienced breast MRI diagnostic radiologist. For each lesion, the boundary of the contrast-enhanced lesion on the first phase post-contrast images was semi-automatically determined using an in-house developed Matlab-based software algorithm that utilizes the MRI signal intensity difference between the contrast-enhanced lesion and its surrounding tissues, resulting in an objective region of interest (ROI) of the lesion (Fig. 1, left) [8]. The determined lesion boundaries on each slice were confirmed by the radiologist. An optimal linear least squares fitting using the last four time points 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. 1, right) [8]. 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. The lesion boundary determinations and the WO volume fraction computations were blinded to the histopathology reports.

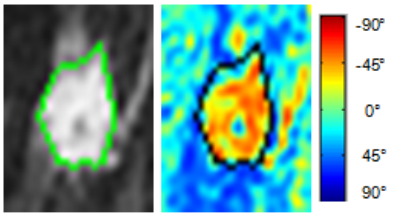

Fig. 1 Left: Illustration of a lesion based on the first-contrast image. Right: Corresponding image of the color-coded degree of slope for the DCE period. A negative degree indicates a WO curve.

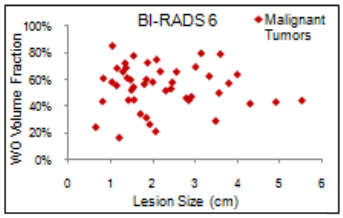

Fig. 2 Distribution of WO volume fraction versus lesion size for the 46 known biopsy-proven malignant tumors (BI-RADS assessment of 6).

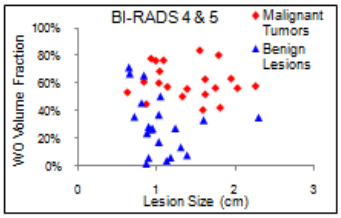

Fig. 3 Distribution of WO volume fraction versus lesion size for the 48 suspicious lesions with BI-RADS assessments of 4 and 5. The lesion types were determined from their histopathology reports.

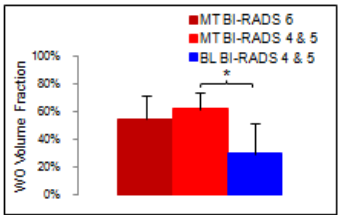

Fig. 4 Comparison of WO volume fraction between the malignant tumors and the benign lesions for the three lesion groups. The error bar denotes the standard deviation. (*: $p=1.45\times10^{-7}$)

Results and Discussion: Figure 2 shows the distribution of WO volume fraction versus lesion size for the 46 malignant tumors (BI-RADS assessment of 6) with a mean and standard deviation of 54.4±16.4 (%). (The lesion size was estimated from the lesion volume using a spherical model.) These 46 malignant tumors include 38 infiltrating/invasive ductal carcinoma and/or DCIS and 8 invasive lobular carcinoma. For the 48 suspicious lesions, the biopsies resulted in 27 benign lesions (BL) and 21 malignant tumors (MT) (the nine highly suggestive of malignant lesions with BI-RADS assessment of 5 and 12 lesions with BI-RADS assessment of 4). Figure 3 shows the distribution of WO volume fraction versus lesion size for the 48 suspicious lesions. The mean and standard deviation of WO volume fraction was 29.3±22.3 (%) for the 27 BL and 60.2±12.4 (%) for the 21 MT, significantly different from each other ($p<2\times10^{-7}$) (Fig. 4). The WO volume fraction showed no significant difference for the two groups of malignant tumors (BI-RADS assessment of 6 versus 4 and 5) ($p>0.06$) (Fig. 4). For the 48 suspicious lesions, the significantly larger WO volume fraction for the MT in comparison to the BL was most likely produced by the hypervascularity associated with tumor angiogenesis, supporting our hypothesis and previous findings [8]. It provides an additional MRI biomarker for improving the characterization of suspicious contrast-enhancing breast lesions, and the biomarker has the potential to improve the computer-based assessment in breast MRI.

References: 1. Kuhl, CK, *et al*, Radiology 211: 101-110, 1999. 2. Bluemke, DA, *et al*, JAMA 292: 2735-2742, 2004. 3. Buadu, LD, *et al*, Radiology 200: 639-649, 1996. 4. Su, MY, *et al*, JMRI, 18: 467-477, 2003. 5. Carmeliet P and Jain RK. Nature 407:249-257, 2000. 6. Orel, SG, *et al*, Radiology 190: 485-493, 1994. 7. Orel, SG, Radiology 211: 5-7, 1999. 8. Huang, J, *et al*, Med. Phys. 38: 5998-6009, 2011.