Diffusion Weighted Imaging in Accurate Classification of Complex Ovarian Masses: A Whole-Tumor Heterogeneity Quantification Approach

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Target Audience: Radiologists, physicists and surgeons with an interest in gynecological MR imaging

Purpose: Differential diagnosis of benign and malignant complex ovarian masses plays a pivotal role in decision making about the treatment strategy and could significantly improve the patient outcome. Diffusion weighted imaging (DWI) and the calculated apparent diffusion coefficient (ADC) have shown great promise in providing non-invasive and sensitive biomarkers of tumor progression in a variety of cancers, such as brain tumors [1]. Nonetheless, in complex masses, qualitative assessment of low signal intensity within solid portion of b_{1000} DW images has demonstrated to be helpful in predicting benignity (high specificity), while the contribution of quantitative ADC is still a matter of controversy [2]. This is mainly because ovarian cancer is a genetically heterogeneous disease and the existence of large inter- and intra-patient heterogeneity could hamper adequate clinical differentiation of complex benign and malignant ovarian lesions. In this regard, quantifying whole-tumor heterogeneity in ADC maps to reveal the differences in patterns of cellular density could be a key point for achieving definitive diagnosis. Inherited from this idea, to probe the heterogeneous nature of complex ovarian masses beyond simple quantitative measures (e.g. mean ADC), we have investigated several textural features within ADC maps of complex ovarian lesions in an unsupervised automatic classification scheme, to introduce the potential predictors of malignancy in complex ovarian cancer.

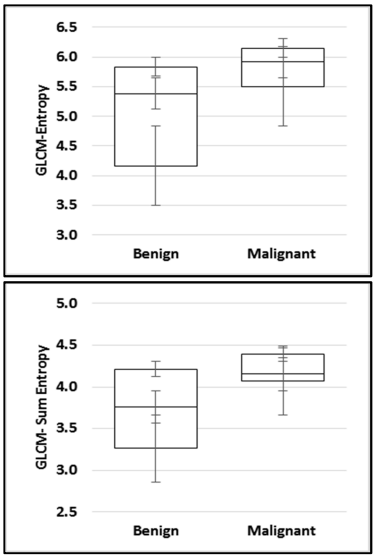

Figure. Box-and-whisker plots for GLCM-Entropy and GLCM-Sum Entropy in the benign and malignant complex ovarian cancers**.**

Materials and Methods: Data Acquisition: Pre-operative DW-MR images of twenty-nine women diagnosed with histopathologically proven complex ovarian masses (13 benign, 16 malignant, 14-70 years, mean age = 35.9) were acquired on a 3T MR scanner (Siemens MAGNETOM Tim TRIO) using a fat-suppressed single-shot GE-EPI sequence and a surface phased array coil, with the following specifications: *TR*/*TE* 4000/72 *m*s; matrix size 108×128; FOV = 253×300; slice thickness 5*m*m; 8 signal averages; Spacing between slices 6mm; at *b*-values of 0 and 1000 s/*m*m^2. ADC-maps were then generated from DW images on the system workstation. Image Analysis and Data Quantification: For each examination, the borders of the most solid portion of the tumor was determined and extracted by an expert radiologist in gynecology on a single slice, to represent the desired region-of-interest (ROI). The ROIs were then scaled down to 64 ADC values to ensure sufficient counting statistics. First and second order statistical texture analysis were then performed to extract histogram and gray-level co-occurrence matrix (GLCM) features. Co-occurrence matrices, representing the probability of having two neighboring pixels with intensities of *i* and *j* were computed for four directions (0º, 45º, 90º, 135º) and averaged to generate rotation-invariant features. Twenty-eight texture features as described by Haralick *et al* [3] were calculated and evaluated. Comparison of the mean values of each computed feature between benign and malignant groups was performed by Student's *t*-test, by assuming equality of variances for independent samples. A *P*-value of less than 0.05 was considered to be statistically significant. Classification: Using each of textural feature and their combinations, classification was performed by linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA) techniques. The performance of the designed classifier was assessed using leave-one-out cross-validation method.

Results: Among all the investigated first-order histogram features, a statistically significant difference was found for energy ($p<0.05$) and entropy ($p<0.05$) measures between benign and malignant patients. Using the second-order texture analysis, the GLCM-Entropy ($p<0.001$), GLCM-Sum Entropy ($p<0.001$), and information measure of correlation ($p<0.05$) differed significantly among benign and malignant patients, among all 28 features of the GLCM. The box-and-whisker plots of the GLCM-Entropy and GLCM-Sum Entropy features with the least p-values are illustrated in **Figure**, showing the capability of these parameters in discriminating benign and malignant groups. **Table** represents the sensitivity and specificity of the mentioned texture features in discriminating benign and malignant complex ovarian cancers. As it is evident, the sensitivity of the texture parameters are high in discriminating benign and malignant groups; nevertheless, the specificity remains fairly low even after using a more advanced (QDA) classifier. It can further be observed that first-order histogram "Energy" and "GLCM-Sum Entropy" measures are the most sensitive, and first-order histogram "Entropy" is the most specific parameters for differentiating benign and malignant cases.

Discussion and Conclusion: The contribution of quantitative ADC in differentiating benign and malignant complex ovarian masses is yet under debate, which could mainly arise from the inherently large inter and intra-patient heterogeneity in complex ovarian tumors. In this work, we strived to investigate the role of ADC maps by accounting for this heterogeneity by means of first- and second-order texture analysis. From first-order histogram analysis, it was indicated that energy and entropy parameters could significantly differentiate the benign and malignant groups. High sensitivity of energy feature in indicating malignancy could be apprehended by considering that energy is a measure of texture homogeneity or uniformity within the selected tumor region. Hence, malignant lesions containing several heterogeneous structures are expected to indicate lower energy values. On the contrary, entropy is a statistical measure of the irregularities within an ROI, which must be larger in malignant lesions. High sensitivity of entropy-based features is indicative of the potential of this measure for diagnosing malignancy. Generally, in previous studies, mean ADC has been calculated on a selected ROI within the tumor to discriminate between benign and malignant ovarian tumors. Nonetheless, this analysis would lead to erroneous tumor characterization because not only ROI placement is user-dependent but also averaging of the pixel values would suppress ADC variations throughout the heterogeneous tumorous region. On the contrary, whole-tumor heterogeneity analysis preserves the information to boost up the sensitivity, in contrast to the ROI-based analysis in which the spatial information is easily lost (averaged out). Regardless, all extracted texture features have low specificity in distinguishing benignity, which is particularly apparent from the inability of a more advanced (QDA) classifier in improving the outcome. It could be inferred that ADC parameters overestimate the heterogeneity, which can be related to the inherent inhomogeneity and irregularity of complex ovarian masses, even in their benign form. This matter calls for incorporating other quantitative imaging techniques such as dynamic contrast enhanced (DCE-) MRI, that can provide specific biomarkers of the cancerous tissues.

Table. Sensitivity and specificity of texture parameters for malignancy prediction

		LDA		QDA		
		Sensitivity (%)	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**p-value**
First-Order Histogram Analysis	Energy	92.3	47.6	92.3	42.9	0.0021
	Entropy	88.5	52.4	88.5	52.4	0.0028
Second-Order GLCM Aalysis	Entropy	84.6	47.6	88.5	42.9	0.0004
	Sum Entropy	96.2	42.8	96.2	47.6	0.0006
	Information Measure of Correlation	88.5	38.1	88.5	33.3	0.0033

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