A radiomics study of textural features using magnetic resonance imaging for classification of breast cancer subtypes

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Abstract. Breast cancer is usually screened using mammography and biopsy is used to confirm diagnosis. Recent radiomics approaches suggest predictive associations between images and medical outcome. This study aims to classify breast cancer subtypes using textural features derived from magnetic resonance imaging (MRI). Thirty-two lesions with histologic results that were definite were studied. A total of 174 textural features were extracted from four MRI sequences (Axial STIR, dynamic contrast enhance (DCE) Phase 2, dynamic contrast enhance (DCE) subtracted Phase 2 and T1-weighted), and analysed using t-test, Kruskal-Wallis and principal component analysis (PCA). Evaluation was done using multinomial logistic regression and leave-one-out-cross-validation (LOOCV) methods. We found 14 texture features that consistently showed significant difference between malignant and normal breast tissues across all MRI sequences. Four textural features were useful in histological status with t-test accuracy of 71.4% and PCA accuracy of 64.3%. In hormonal receptor status, only five textural features were useful. The accuracies were also found to be poorer with 46.4% accuracy based on Kruskal-Wallis method and 46.4% accuracy using PCA method. As this is a preliminary study, the analysis should be extended to a larger sample size to accurately determine the possibility of clinical diagnosis.

1. Introduction
Breast cancer is a common disease impacting towards 2.1 million women each year [1]. In Malaysia, the prevalence of breast cancer is 31%, ranking highest compared to other cancer subtypes [2]. In current practice, breast cancer is usually detected using mammography and diagnosis is confirmed via biopsy and immunohistochemistry (IHC) reports. While biopsy is very invasive, medical imaging such as magnetic resonance imaging (MRI) is able to visualize the whole tumour volume and the breast anatomy non-invasively. IHC aids in the characterisation of breast cancer; yet it also has certain limitations. The tumour is usually heterogeneous; hence, using biopsy to characterize tumour tissue is subject to sample uncertainty [3]. With regard to MRI, the subjectivity of reader visual analysis leads to the possibility of errors and uncertainties [4]. The hypothesis of the radiomics approach is that characterisation of the whole tumour may offer predictive probabilities or diagnostic associations.
between medical outcomes and images [5]. Texture analysis in medical imaging evaluates image patterns and is often termed by numerous adjectives such as fine or coarse, irregular or regular, rough or smooth [6]. These patterns can then be correlated with pathological and physiological stages, and the tissues properties. Texture analysis has been used to distinguish normal and cancerous regions using post-contrast MRI images [7] and for the detection of microcalcification susceptibility effects [8].

In this project, we attempted to determine the textural features that are useful for breast cancer detection, and to perform classification of breast cancer subtypes based on their histopathological status and receptor status.

2. Materials and Methods

2.1. Patient data

MRI data of 29 patients from University of Malaya Medical Centre with approved ethics (MECID No 201796-5552) were used for this project. All MRI scans were performed using a 3T MRI (Signa, GE, Wisconsin, USA) scanner. Table 1 summarised the type of cases studied. Four image sequences were selected (Axial STIR, dynamic contrast enhance (DCE) Phase 2, DCE Phase 2 subtracted and T1-weighted) for texture analysis (Figure 1). Contours of 3D tumour region were defined by a radiology registrar and verified by a radiologist (with 10y experience in reporting MRI images). 3D binary masks were created for tumour segmentation using semi-automated feature in ITK-SNAP, ver. 3.8.0 beta (Researchers of Upenn and UNC). In comparing normal and malignant tumours, a contralateral comparison was done among patients with unilateral breast tumours. An equivalent volume of normal breast tissue region was delineated on the contralateral side of the breasts.

Table 1. Summary of the type of cases studied

| Classification      | Cases   | Reasoning                                                                 |
|---------------------|---------|---------------------------------------------------------------------------|
| Normal vs. Malignant| 25 patients | 25 contralateral comparison among 25 unilateral tumours (1 patient with single breast omitted) |
| Histopathological status | 28 lesions | 23 Ductal type, 5 Lobular type |
| Receptor status     | 32 lesions | 20 HR+, 5 TN-, 7 Others (5 Hybrid, 2 HER2+) |

Figure 1. MRI breast image in (a) Axial STIR, (b) DCE Phase 2, (c) DCE Subtracted Phase 2, (d) T1-weighted and (e) image of segmented ROI overlaid with MRI breast image in STIR. Red arrows point to the malignant tumour region.

A total of 172 texture features (43 x 4 MRI image sequences) based on: Global features, Gray-level co-occurrence matrix (GLCM), neighbourhood gray-tone difference matrix (NGTDM), gray-level size zone matrix (GLSZM) and gray-level run-length matrix (GLRLM) and 4 non-texture features based on: volume, size, solidity and eccentricity from Vallieres et al, 2015 [9] were extracted using MATLAB R2017a (Mathworks Inc, MA, USA). Thereafter, the data was normalized via group mean and standard deviation. For normal/malignant analysis Wilcoxon sign rank test was used. As for histopathological status analysis, t-test and PCA was used as independent methods of feature selection.
or reduction. In the analysis of receptor status, Kruskal-Wallis and PCA were used instead. In all status cases, multinomial regression was used to classify the selected or reduced features, and LOOCV analysis was also performed. In all cases, statistical significance was set at $p<0.05$.

3. Results and Discussion
A large number of texture features showed significant difference among normal and malignant breast texture features, including 28 features in Axial STIR, 36 features in DCE Phase 2, 42 features in DCE subtracted Phase 2, and 20 features in T1-weighted MRI. However, only 14 features were consistently useful to differentiate normal and malignant breast tissues. Table 2 shows the baseline values of the 14 texture features that were consistently useful for all MRI sequences. In general, the malignant breast tissues are generally brighter and more heterogenous compared to the normal contralateral breasts.

Table 2. Baseline value of texture features for normal/malignant breast tissues with significant differences (median value)

| Texture | Axial STIR | Phase 2 | SubPhase 2 | T1-weighted |
|---------|-----------|---------|------------|-------------|
| Global  | Skewness  | 0.8/-0.2| 1.1/0.0    | 1.3/0.1     | 0.9/-0.7    |
| GLCM    | Sum Average (x10^3) | 1.0/2.0 | 1.1/2.1 | 0.1/0.2 | 0.1/0.3 |
|         | Auto Correlation (x10^4) | 0.9/1.8 | 0.6/2.0 | 0.2/1.7 | 0.8/2.7 |
| GLRLM   | HGRE(x10^5) | 1.0/1.8 | 0.6/2.0 | 0.3/1.7 | 0.9/2.7 |
|         | SRHGE(x10^4) | 1.0/1.7 | 0.6/2.0 | 0.3/1.7 | 0.9/2.6 |
|         | LRHGE(x10^4) | 1.0/1.9 | 0.7/2.0 | 0.3/1.7 | 0.9/2.8 |
|         | GLV(x10^5) | 0.3/0.8 | 0.4/1.6 | 0.1/1.3 | 0.1/0.3 |
| GLSZM   | ZSN | 0.6/0.7 | 0.7/0.8 | 0.7/0.8 | 0.7/0.8 |
|         | HGZE(x10^5) | 1.1/1.7 | 0.7/1.9 | 0.3/1.7 | 0.9/2.6 |
|         | SZHGE(x10^5) | 1.0/1.5 | 0.5/1.7 | 0.3/1.6 | 0.9/2.2 |
|         | GLV(x10^4) | 0.1/0.3 | 0.1/0.7 | 0.2/5.7 | 0.1/0.9 |
|         | ZSV(x10^5) | 0.1/0.2 | 0.2/0.4 | 0.1/0.4 | 0.2/0.4 |
|         | Coarseness | 0.3/0.6 | 0.2/0.3 | 0.1/0.3 | 0.2/0.4 |
|         | Busyness | 0.3/0.1 | 0.5/0.1 | 0.3/0.0 | 0.4/0.1 |

**Skewness**: Tumours are negatively skewed; **Sum Average**: reflects the average intensities of the image – Tumours are brighter; **Auto Correlation**: reflects the gray-level linear dependencies. Tumours are more heterogeneous; **HGRE** (High Gray-Level Run Emphasis) is large for the image with high gray level values – Tumours are brighter. **SRHGE** (Short Run High Gray-Level Emphasis) is large for images with many short runs and high gray level values – Malignant tissue has more bright spotted features. **LRHGE** (Long Run High Gray-Level Emphasis) is large for images with many long runs and high gray level values – Tumours with big blobs of bright patches. **GLV** (Gray-Level Variance) measures gray level variance – tumour has larger heterogeneity. **ZSN** (Zone-Size Non-uniformity) measures the similarity of the size of zones throughout the image. If the sizes of zones are similar, the value is small. **HGZE** (High Gray-Level Zone Emphasis) is large for image with high gray level values – Tumour appears brighter. **SZHGE** (Small Zone High Gray-Level Emphasis) is large for the image with many small size zone and high gray level values – Tumour has more area of bright small spotted zones. **GLV** measures the gray level variance – Tumour more heterogenous in terms contrast. **ZSV** measures the zone size variance - Tumour more heterogenous in terms of blob size; **Coarseness** measures the granularity within an image based on differences between each voxel and the neighbouring voxels in adjacent image planes. Tumour is more heterogenous; **Busyness** measures the rapid changes in intensity from one pixel to its neighbor – Tumour is inhomogeneous.
In classification of the hormonal receptor status, only five T1 textural features (LRE, RLN, RP, SZE and Complexity) from T1-weighted MRI showed significant differences. Classification accuracy using Kruskal-Wallis feature selection was found to be 46.4%. Classification accuracy using PCA feature reduction was found to be 43.8%. Both methods yielded accuracies poorer than the prevalence of the largest category (HR+ at 62%).

Four features (Contrast, Correlation, Dissimilarity and Complexity) were able to consistently classify the breast lesions according to their histopathological groups. Accuracy was 71.4% and 64.3% using t-test and PCA respectively. Both methods yielded accuracies poorer than the prevalence of the largest category (ductal carcinoma category at 82%).

4. Conclusions
Fourteen texture features were useful to differentiate tumours from normal breast tissues. Findings of texture features correlate with radiological observation of breast tumours, whereby tumours are highly contrasted and heterogeneous. The number of texture features reduces to five for classification of hormonal receptor response cancer subtypes. Only four features were useful to distinguish the ductal from lobular carcinomas. The accuracy of this method is only 70% at best, due to the limited sample size. The limited numbers of textural features were only focused in pixel intensity based features. A promising direction for future might be in higher dimensional textural features such as wavelets and Fourier features [10].

5. References
[1] World Heath Organization 2018 Breast Cancer. Retrieved November 16, 2018, from World Health Organization: http://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/
[2] The Malaysian National Cancer Registry Report (2007-2011) Retrieved November 16, 2018, from https://kpkesihatan.com/2016/12/07/the-malaysian-national-cancer-registry-report-mncr-2007-2011/
[3] Yip S F and Aerts H J 2016 Phys. Med.Biol. 61(13) 155-60
[4] Yang X Y and Knopp M V 2011 J. Biomed.Biotechnol. 732848 732-48
[5] Kumar V, Gu Y, Basu S, Berglund A, Eschrich S A, Schabath M B, Forster K, Aerts H J, Dekker A, Fenstermacher D and Goldgof D B 2012 Magn. Reson. Imat., 30(9) 1234-48
[6] Tuceryan M and Jain A K 1998 Handbook of Pattern Recognition and Computer Vision ed P L Chen CH (New Jersey: World Scientific Publishing Co.)p 207
[7] Gibbs P and Turnbull L W 2003 Magn. Reson. Med. 50(1) 92-8
[8] James D, Clymer B D and Schmalbrock P 2001 J. Magn. Reson. Imat. 13(6) 876-81
[9] Valliêres M, Freeman R C, Skamene S and El Naqa I 2015 Phys. Med. Biol. 60(14) 5471-96
[10] Thawani R, McLane M, Beig N, Ghose S, Prasanna P, Velcheti V and Madabhushi A 2018 Lung Cancer 115 34-41

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