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Radiomics Analysis of MRI for Predicting Molecular Subtypes of Breast Cancer in Young Women

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ABSTRACT

Breast cancer in young women is commonly aggressive, in part because the proportion of high-grade, triple-negative (TN) tumor is too high. There are certain limitations in the detection of biopsies or surgical specimens which only select part of tumor sample tissue and ignore the possible heterogeneity of tumors. In clinical practice, MRI is used for the diagnosis of breast cancer. MRI-based radiomics is a developing approach that may provide not only the diagnostic value for breast cancer but also the predictive or prognostic associations between the images and biological characteristics. In this work, we used radiomics methods to analyze MR images of breast cancer in 53 young women, and correlated the radiomics data with molecular subtypes. The results indicated a significant difference between TN type and non-TN type of breast cancer in young women on the radiomics features based on T2-weighted MR images. This may be helpful for the identification of TN type and guiding the therapeutic strategies.

1. INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancers, with an estimated 266,120 new cases of invasive breast cancer diagnosed in the United States alone[1]. Approximately 6-7% of woman diagnosed with breast cancer in the United States are 40 years or younger[2]. Young women with breast cancer face more difficulties than older woman, for example, a higher risk of genetic susceptibility, earlier menopause, fertile and sexual life, and so on[3]. Because of the relative low frequency of screening for early detection, young women are prone to come upon higher stage, symptomatic breast cancer, with has been documented to lead to worse outcomes for the patient when compared to older women with breast cancer [4].

Breast cancer can be classified into subtypes, which are distinguished by different characteristics in their gene expression patterns [5]. Molecular type of breast cancer grouped through gene expression profiling was first described by Perou[6]. Immunohistochemistry techniques then seemed quite accurate for the classification of breast cancer molecular phenotype, at a much lower cost than genetic expression testing with microarrays, so the Expert Panel of the 12th St Gallen International Breast Cancer Conference (2011) accepted a new approach to the classification of patients for therapeutic purposes based on the recognition of intrinsic biological subtypes [7]. The classification of breast cancer includes four categories in terms of hormone receptor, HER2 status, and Ki-67 labeling index, taking no account of clinicopathologic features. Such classification of breast cancers is both simple and practical, and generates group-specific information that is remarkably useful in clinical ground. Identification of subtypes benefits to improve precision therapy and to evaluate prognosis in breast cancer patients. For instance, anti-HER2+ therapy is useful for breast cancer with overexpression of HER2, higher rate of radical treatment has been found in pure HER2 and triple-negative patients, luminal A subtype patients show significantly lower mortality rates compared to other

subtypes of breast cancer[8], and luminal A and B phenotypes have a relatively good prognosis, whereas triple-negative and HER2 tumors show extremely poor prognosis and a higher recurrence and metastasis rates[9].

At present, using imaging techniques to detect different molecular types of breast cancer has become a hot topic. Medical imaging in the form of mammography, ultrasound, and magnetic resonance imaging (MRI) can provide some information of molecular subtypes of breast cancer, for example, triple negative tumors were more frequently unifocal and mass-like lesion, round shape, smooth margin, and rim enhancement, and luminal A were more frequently irregular shape and spiculated or irregular margin[10]. However, all of these studies used visual assessment by radiologists, which had a great variability and depended almost entirely on the experience of radiologists.

Recent research in the medical imaging field shows that radiomics, which is described as the high-throughput extraction of large amounts of medical image features from radiographic images, to be useful in biopsy, microscopy and even DNA analysis[11]. Currently, several research groups are developing radiomic "feature" sets to symbolize tumors. These mathematical features provide methods to characterize the size, shape, texture, intensity, margin, and other sides of the extracted features of nodules and lesions, with the eventual purpose of separating benign from malignant nodules, evaluating response to therapy, and linking imaging with genomics. Grimm *et al.*[11] demonstrated that semi-automatically extracted breast MRI features are correlated with both luminal A and luminal B molecular subtype breast cancers. Mazurowski's work[12] used computer extracted features to detect luminal B subtype only, which was of great importance because differentiating between luminal A and luminal B breast cancers is critically crucial for treatment planning.

Since many newly diagnosed breast cancer patients undergo breast MR imaging before final treatment, it would be a valuable additional diagnostic tool if molecular subtypes could be identified from medical images. In this work, we use radiomics features to analyze MR T2-weighted images (T2WI) and try to identify the inner correlation between radiomics data and molecular types in young breast cancer. MR imaging features associated with molecular subtypes of breast cancer may be used as an adjunct to help guide clinicians in treatment planning.

2. METHODS

2.1 Patient Population

All methods were carried out in accordance with the approved Institutional Review Board (IRB) protocol and the relevant guidelines and regulations. In this retrospective study, MRI images of 53 breast cancer women, with ages between 27 and 40 years, an average age of 35.27 years, were reviewed.

2.2 Patient Histological Data

Molecule subgroup classification was based on both presence and absence of characteristic critical proteins or gene substitutes of tissue pathology. Breast cancers were divided into four molecule subtypes defined according to the following standards: luminal A (N_A = 10, ER positive and/or PR positive, HER2 negative, and low/intermediate grade on Ki-67); luminal B (N_B = 32, ER positive and/or PR positive and HER2 positive; or ER positive and/or PR positive and HER2 negative and high grade on ki-67); HER2 (N_{HER2} = 4, ER negative, PR negative, and HER2 positive); and triple negative (N_{TN} = 7, ER negative, PR negative, and HER2 negative).

2.3 Image Acquisition, Processing, Segmentation and Feature Extraction

A complete radiomics project workflow includes the following stages: identifying a question and designing patient cohort, develop robust image preprocessing, segmenting the regions of interest (ROI) in the images, exacting the features, statistical analysis or modeling[13].

2.3.1 Imaging Data Acquisition

MR imaging examinations were performed with the patients in the prone position by using a GE 1.5T MRI scanners or two Philips 3.0T MRI scanners with breast surface coils. Axial T2-weighted images, T1-weighted images, DWI, dynamic enhanced images were performed. Each MR had a slice thickness of 2-5 mm, matrix of 80x80-256x256, field of view (FOV) of 35cm, depending on different scanners and scan sequences.

2.3.2 Imaging Data Processing

After the acquisition of images, all T2-weighted images were loaded into ImageJ to form a High Dynamic Range Imaging (HDR imaging), then HDR imaging were input into AnalyzePro 1.0 (AnalyzeDirect, Overland Park, KS) to perform the segmentation.

2.3.3 Imaging Data Segmentation

The T2-weighted MR images were segmented by a trained radiologist with 14 years of experience in radiology reading breast MR imaging to define the region of breast tumor (Figure 1). Region of interest of segmentation was independently delineated for all tumor regions in T2-weighted images, without avoiding cystic degeneration or necrotic areas. For manual software tools, tumors were contoured using a manual trace tool (thresholding in 3D-Slicer) in a slice-by-slice mode in the transverse plane. Radiologists could also observe and edit the tumor contour in the coronal and sagittal planes.

Accurate segmentation is an important step of the radiomics workflow. Variation in contouring can highly affect the extracted feature values, which would undoubtedly influence subsequent steps in the radiomics workflow. Segmenting a single slice significantly improves efficiency when manual segmentation is used, but the extracted ROI may not represent the entire tumor, hence, we used 3D-model to perform the segmentation of the tumor. Automated tools can significantly affect the time it takes to segment the ROI, which is a key consideration when data from thousands and hundreds of patients will be used. To overcome this limitation of manual segmentation, several semi- and fully automated methods have been used for segmentation. Parmar[14], for example, implemented a semiautomatic region-growing segmentation algorithm in the 3D-slicer platform and showed that this approach was much more reproducible than manually drawn boundaries. Owens[15] evaluated the uncertainty of radiomics features segmented from both manual and semi-automatic segmentation due to intra-observer, inter-observer, and inter-software reliability. They found the fact that, using semi-automatic segmentation such as LSTK, implementers without formal clinical training can draw contours that are roughly comparable to manually drawn contours drew by formally trained physicians. Although manual segmentation requires a significant amount of time (approximately 20 min per patient) and shows a degree of variability over time and between raters, to date, manual segmentation has been still considered the gold standard for analyzing volumes, and many successful radiomics studies used manually-delineated contours [16, 17]. In our research, we performed the manual method for the segmentation since the number of patient was not large in the study and did not require too much labor.

2.3.4 Radiomics Features Extraction

Radiomics features used in the study included eight shape- and size-based features, textural features (21 features with 13 directions), wavelet features (14 features with 8 filter sets), and two morphological features for a total of 538 features. All of the features were described in Aerts 2014[18] with the exception of the morphological features. These two features were created by altering two previously published radiomics features[19]: mean tumor margin gradient and variance of tumor margin gradient. The tumor margin gradient was defined as the intensity gradient across the border between the tumor and normal tissue, calculated by finding the gradient at every pixel along the tumor side of the margin and the nearest non-tumor pixel. The mean and variance of these gradients were calculated and used as features.
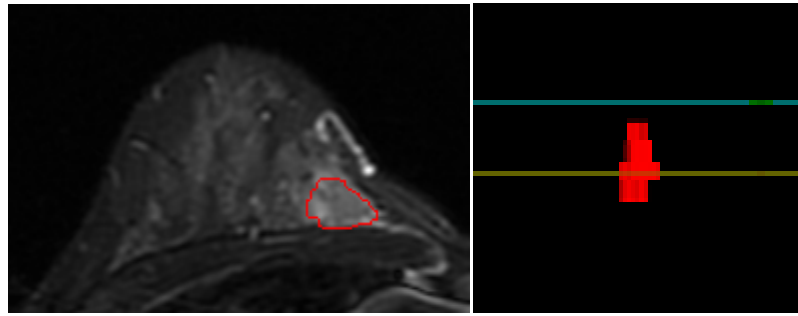
A.   MR image of triple negative (TN) breast cancer of a patient.
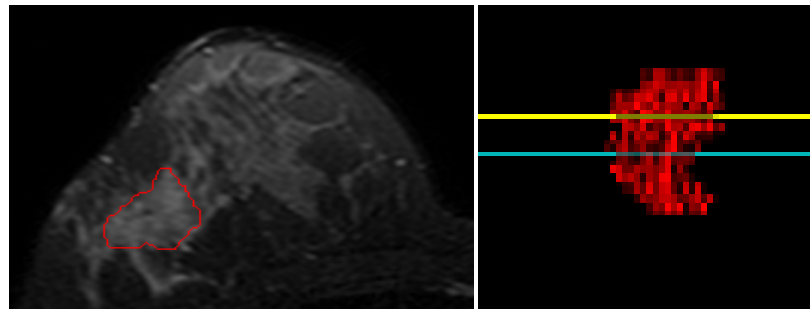
B.   MR image of luminal B breast cancer of a patient.

Figure 1: Segmentation using T2-weighted MR images of a 37-year-old woman with triple negative breast cancer (Fig 1A) and a 35-year-old woman with luminal B breast cancer (Fig 1B). Segmentation provided by a trained radiologist. The lesion in the breast is visible on the image slice (left, red outline) and the three-dimensional (3D) visualization of the lesion (right).

2.4 Radiomics Feature Analysis

Patients were compared in 8 group pairs: (i) Luminal A vs.Luminal B, (ii) Luminal A vs. Triple Negative, (iii) Luminal A vs. Her2, (iv) Luminal B vs. Triple Negative, (v) Luminal B vs. Her2, (vi) Her2 vs. Triple Negative, (vii) Luminal A, B, and Her2 patients vs. Triple Negative, and (viii) Luminal A and B patients vs. Her2. P values were calculated using a t-test with a 95% confidence level to determine significance.

3.   RESULTS

3.1 Patient Population

53 women with the diagnose of young breast cancer (YBC) (mean age 35.27±4.06[SD], range: 27-40 years) were included in this study, with the molecular subtypes of luminal A, luminal B, HER2, and triple negative, accounting for 18.87% (10/53), 60.3% (32/53), 7.5% (4/53), 13.2% (7/53), respectively.

3.2 Feature Analysis

The number of significant features found using the Student t-Test between various pairs of groups is shown in Table I. The greatest number of significant features were found when the triple negative patients were compared against the other patients. Wavelet features provided the majority of those features found significant. A heat map showing several of the *p*-values for several Wavelet features across several comparisons is show in Figure 2. Figure 3 shows box plots with the means of several of the significant features.

Table 1. Number of significant features for each category using a T-Test between different subtypes.

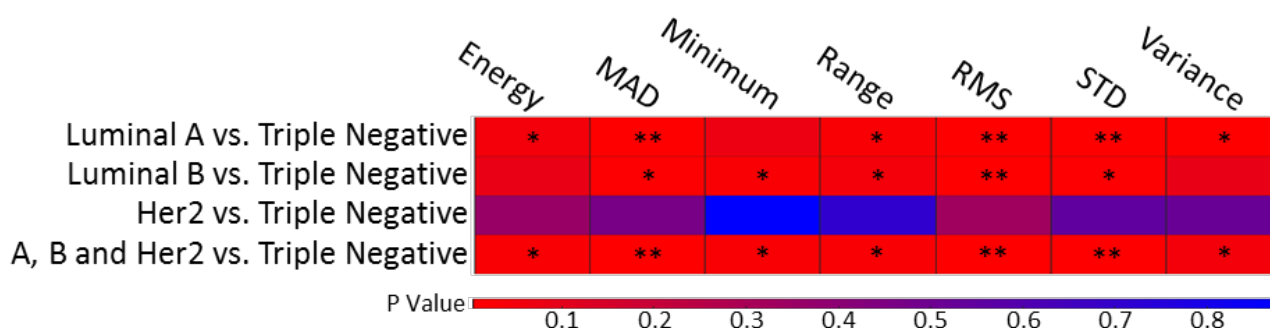| Comparison	Shape and Size	GLCM	Wavele	Morpholog	Total
Lum. A vs. Lum. B	0	0	0	0	0
Lum. A vs. Triple	1	0	22	0	23
Lum. A vs. Her2	0	0	9	0	9
Lum. B vs. Triple	0	0	42	2	44
Lum. B vs. Her2	0	0	1	0	1
Her2 vs. Triple Neg.	0	0	2	0	2
Lum. A, B & Her2 vs. Triple Neg.	1	9	44	2	56
Lum. A & B vs. Her2	0	0	1	0	1

Figure 2. Heat map of T-Test p values (* P Value < 0.05, ** P Value < 0.01) for several comparisons using select features from the LLH Wavelet Statistics. **MAD:** Mean Absolute Deviation, **RMS:** Root Mean Square, **STD:** Standard Deviation.

4. DISCUSSION

In this study, we investigated the utility of radiomics features extracted from T2-weighted images of pretreatment MRI to evaluate the molecular subtypes of breast cancer in young women. To the best of our knowledge, this is the first work to show results for the associations between T2-weighted MRI based radiomics and molecular subtypes of breast cancer in young women without time series data.

In our research, the greatest number of significant features were found when the triple negative breast cancer (TNBC) patients were compared against the other patients, which means that the triple negative molecular subtype is associated with computerized MR imaging features extracted from pre-contrast T2-weighted images.

The definition of TNBC applies to all breast tumors that lack the expression of ER, PR and HER2, all of which are molecular targets of therapeutic agents. Patients with TNBC typically have a relatively poorer outcome compared with other breast cancer subtypes owing to an inherently aggressive clinical behavior and a lack of recognized molecular targets for therapy. The lack of molecular targets makes that chemotherapy is still the primary established treatment

option for patients with early-stage and those with advanced-stage TNBC[20]. The vast heterogeneity of TNBC also extends to the tumor immune microenvironment, which displays a full array of different levels of lymphocyte and monocyte infiltration and activation of inhibitory checkpoints such as PD-1/PD-L1. Demonstrating the subtype of breast cancer is critical for surgical and radiation planning, as well as appropriately routing patients who will benefit from neoadjuvant chemotherapy (NAC). Improved understanding of TNBC biology has led to increasing use of NAC.
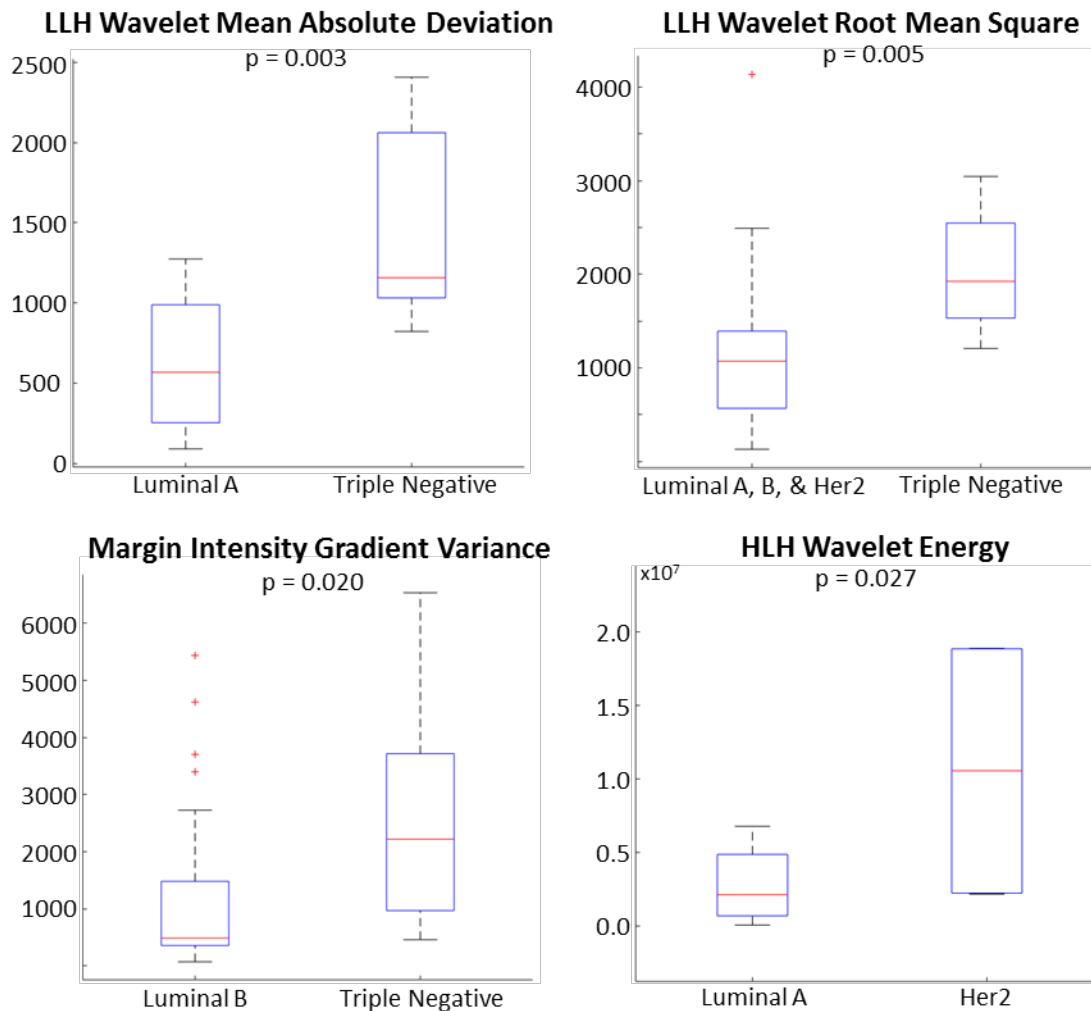

Figure 3. Box plot comparisons of the mean values for select features and groups. Horizontal blue lines indicate the 25th and 75th percentiles, while the red mark represents the mean. The non-outlier extremes are depicted by the whiskers. P values are shown for each chart.

Since the treatment of TNBC is more difficult than the other three subtypes, it is important to identify the triple negative patients. If the subtypes could be predicted without the utility of biopsy, this also reduces the risk of infection to the patient and can decrease the time needed for diagnosis. TNBC lacks the typical suspicious radiologic features of breast cancer; namely irregular mass shape, spiculated margins and associated suspicious calcifications, so it is very difficult to make diagnosis on conventional medical imaging. Processing such radiomics features is without added cost, and if similar information can be achieved through the use of imaging studies that are already being performed, then this would be of value to patients and clinicians.

In terms of preprocessing steps, typical radiomic features extracted included the size of the lesion (e.g., volume, maximal diameter, and size of bounding box), local (e.g., roughness) and global (e.g., eccentricity) shape descriptors, lesion intensity (e.g., average, median, maximum, minimum, and standard deviation voxel values), margin (e.g., edge gradients), and texture (e.g., those based on GLCMs and wavelets)[21]. In this work, we use radiomics features, such as shape and size, GLCM, wavelet, morphology, to measure the inner characteristic of tumor. The most useful set of features in our study belonged to wavelet statistics, with the greatest number of statistically significant features being observed when Luminal A, Luminal B, and Her2 patients were grouped together and compared against triple negative patients. The wavelet transform is similar to the Fourier transform, which represents signals as a summation of sinusoidal building blocks, or basis functions. One crucial difference, however, is that the wavelet transform is localized in both frequency and time, while the standard Fourier transform is only localized in frequency. That is, the Fourier transform tells what frequencies are present in a signal, and the wavelet transform tells what frequencies are present and when. Wavelet features respond to image inhomogeneity from different aspects[22], for example, contrast reflects the clarity of the image and the texture of the groove depth, entropy quantifies complexity of the image, IDM reflects the sharpness of the image. The representation of these features in this study indicates the TNBC are more likely to be heterogeneous, this can explain why TNBC lesions have more biologically proliferating, and hence have more voxels of different uptake that appears to be more inhomogenous.

Our study has several limitations. One limitation of the present study was that the work was retrospective, without standardization process for image acquisition, including image resolution, field of view, slice thickness, and so on. Data from different MR scanners might increase the uncertainty in calculating features, therefore, there might be bias between different image sets. Second, the number of this dataset was small, this was due to the lack of young women with breast cancer. Even in the era of big data, good patient datasets are difficult to build. To expand radiomics research, larger cohort study will be necessary. Third, patients above 40 years old were not included in our study to make the comparative study with breast cancer patients in young women. Finally, other images, such as enhancement images, diffusion-weighted images, were not analysed. Radiomics features based on these images may provide additional value to further improve the diagnostic performance.

5. CONCLUSION

In this study, we proposed an MRI-based radiomics approach for distinguishing the subtypes of breast cancer. The method significantly improved the ability to classify triple-negative breast cancer from other molecular types of breast cancer in young women. Wavelet features provided the majority differential diagnostic value among those features found significant. The radiomics approach may be used as predictive markers for diagnosis, prognosis, and therapeutic planning of breast cancer in young women.

Future work will expand the number of patients used and compare the subtype evaluation to benign disease. Other MRI sequences will also be included in the analysis.

ACKNOWLEDGMENTS

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