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High histological grade breast cancer morphological evaluation on mammogram using the box-counting fractal dimension

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Abstract

To evaluate the high-grade breast cancer morphological complexity on mammogram. We conducted a retrospective study using an open source data got from *figshare repository*. These anonymized data were collected and used for a study approved by the institutional review board. Cranio-Caudal and Medio-lateral mammograms and their tumor segmented images from 66 patients subdivided in two groups high histological grade (n=23) low-grade (low and intermediate, n=41). From breast cancer image segmentation, we extracted fractal dimension using *Fraclac*, plugin of *ImageJ* software based on box-counting method. For our analysis we used comparatively the fractal dimension from cranio-caudal (CC) and medio-lateral (MLO) images. We summarized the fractal dimension of our cohort using boxplot and performed the Wilcoxon non-parametric statistic for fractal dimension comparison of two groups (High-grade and low-grade). There was not difference between CC (mean ± std= 1.1583±0.067) andmLO (mean ± std =1.1551±0.055) breast cancer fractal dimension. For the high-grade differentiation, CC andmLO images fractal dimension were contributed respectively at a little difference but without statistically difference (*P* value=0.438 and 0.435). High-grade fractal dimensions mean were respectively 1.142±0.044 and 1.144±0.075 for CC andmLO images against 1.166±0.050 and 1.160±0.057 for low-grade. It had been recorded a lower mean value of fractal dimension for high-grade breast cancer without statistically significant. This finding shows that the high-grade breast cancer tends to have a regular shape.

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Introduction

Breast cancer is the most common cancer in women and a leading cause of cancer death worldwide (Bray *et al.,* 2018). Management of breast cancer relies on the availability of robust clinical and pathological prognostic and predictive factors to guide patient decision making and the selection of treatment. Histological grade is one of important prognostic factor. It is based on the degree of differentiation of the tumor tissue and based on the evaluation of three morphological features: (a) degree of tubule or gland formation, (b) nuclear pleomorphism, and (c) mitotic count. It is used to categorize breast cancer patients in three clinical groups grade I (low), grade II (intermediate) and grade III (high) (Elston and Ellis 1991). High-grade breast cancer is recognized as more aggressive cancer type and is the worst survival prognostic and need a specific treatment (WHO 2006; Rakha *et al.,* 2008b, a).

To date, the histological grading is one of popular method used to categorize breast cancer patients in therapeutic groups (low and high risk). Whereas, this method has been described as subjective method with sometimes inter-observer variability (Gilchrist *et al.,* 1985; Theissig *et al.,* 1990).

In this context, some authors attempted to describe the high-grade breast cancer aspect on medical image in order to allow its a better identification for the clinician. Regarding mammogram, Lamb *et al.* found that classical appearance of a low or intermediate grade tumor is a speculated mass on mammography (Lamb *et al.,* 2000). SHIN *et al.* 2011 had also attempted to describe it morphological aspect on mammogram because mammography is one of the primary breast imaging modalities used in breast cancer diagnosis. They found that having Fairly slow developing grade I tumors (low grade) and grade II tumors (intermediate grade) presents a stroma reaction resulting in imaging by spicules while high grade with rapid evolution, do not develop a stroma reaction and has a round shape (Shin *et al.,* 2011). The findings of both previous studies suggested that histological high-grade breast cancer tends to have a particular margin.

Due to development the Computer Aid Diagnosis (CAD) based on mammography several reliable quantitative features had been used to describe breast cancer morphological characteristic. In this context, shape factors such as compactness, fractional concavity, spiculation index, and a Fourier-descriptor-based factor have been proposed for breast lesion classification (Rangayyan *et al.* 1997, 2000). Latter fractal dimension had been used in the same purpose and it allowed to get a result better than with previous features for the breast cancer differentiation from benign lesion (Rangayyan and Nguyen 2007). Fractal geometry is a powerful tool for describing and modeling natural objects. Most of these applications employ fractal dimension, a measure that captures the so-called complexity of the object, a fundamental descriptor of analyzed objects represented in a digital image. In this context, complexity expresses the level of detail detected at different scales. This measure is immediately related to physical characteristics, which are fundamental to the description and identification of objects, even in our human vision system (texture analysis using fractal). In last decade, following success of CAD, several studies used medical image quantitative features in order to decrypt cancer biology (Sanduleanu *et al.,* 2018). Recently Fan *et al.* and Huang *et al.* extracted quantitative features from medical image to find those which are relevant to breast cancer histological grade (Huang *et al.,* 2018; Fan *et al.,* 2019). In these previous studies, fractal dimension was not used, while it showed a better potential for the differentiation of the breast tumors in according to their margin characteristic. Based on hypothesis that the high-grade breast cancer presents a particular margin, we used in this study, the fractal dimension to evaluate its morphological complexity on mammogram and find the importance of this quantitative feature in its differentiation from other grades (low and intermediate).

Material and methods

Patients data

We conducted a retrospective study using an open source data got from figshare repository (Trevino 2018). These anonymized data were collected and used for a study approved by the institutional review board.

It aimed to establish an association between digital mammography radiomic and breast cancer Oncotype DX and PAM50 recurrence scores. The study englobes a total of 71 breast cancer cases with clinicopathologic informations (age, TNM grading, ER, PR, and HER2 status), digital mammograms (cranio-caudal CC and medio-lateral obliquem LO), microarray data and tumor segmentation on mammograms images.

A digital mammography system (Selenia, Hologic, Bedford, MA), with an automatic intensity adjustment was used to acquire mammogram of 70 microns per pixel and 12-bits grayscale for codification. Manuel segmentation of tumors were performed by an experienced breast radiologist (Tamez-Peña *et al.,* 2018). Five (05) patients were excluded because their histological grading status is missing. Amongst the sixty-six (66) patients of our cohort, twenty-three (n=23) were high-grade, thirty-seven (n=37) were intermediate grade, and six (n=6) had low histological grading status with respective mean age of 50, 50.5 and 54 years.

Fractal dimension determination

Dicom Mammograms and tumor segmentation images were decompressed with the open source Dicom viewer software MicroDicom 2.7.9. Tumor segmented images were rescaled between 0 and 1 grayscale with image processing software ImageJ (Abràmoff *et al.,* 2004; Schneider *et al.,* 2012; 'ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2018.' 2018). We used box-counting method to perform fractal dimension based on tumor segmented image.

In box counting, data are gathered by laying boxes over a digital image as a series of grids of decreasing box size, then the number of boxes that fall on the image (*NC)* and the size of each box (*C*) are recorded. *C,* the relative scale, can be considered as 1/box size, because the image size is a constant. From this series of paired data, one infers the DB as the slope of the log-log plot of C^{-1} on the x -axis and *NC* on the y -axis (Fig. 1) (Karperien *et al.,* 2008). In our study we used *FracLac* V.2.5 (Karperien 2015) a special ImageJ plugin for the box-counting fractal analysis.

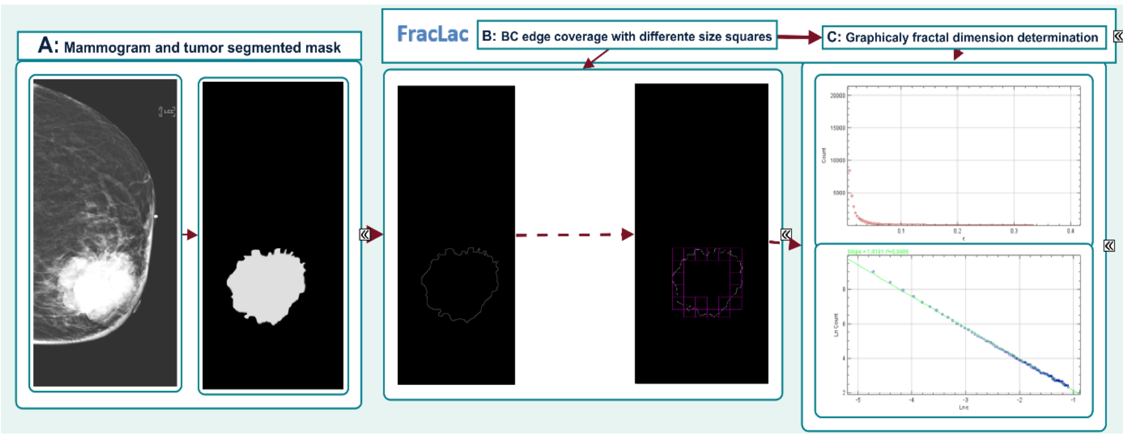

Fig 1. Fractal dimension extraction workflow.

Statistical analysis

For this step, we performed our analysis using comparatively the fractal dimension from cranio-caudal (CC) and medio-lateral (MLO) images. We summarized the fractal dimension of our cohort using boxplot and performed the Wilcoxon non-parametric statistic for fractal dimension comparison of two groups (High grade and low grade). Statistical open source software R-3.4.2 had been used. All statistical tests were considered statistically significant if *P* value is less than 0.05.

Results

Table 1 shows that among twenty-three (23) high-grade breast cancer cases, eleven (11) had less than fifty (50) years old and twelve (12) were older than fifty (50) years. In low histological grade group we found twenty three (23) patients for under 50 years and twenty (20) for more than 50 years. In our cohort there is not a dependence between breast cancer histological grade and patients age.

Table 1. Histological grade in function of patient age.

	Age<50		
Histological grade	Yes	No	Total
High	11	12	23
Low	23	20	43
Total	34	32	66

Fig. 2,3 and 4. shows respectively the fractal dimension distribution comparison between:

- CC andmLO images of each patient;
- high and low histological grade using CC image;
- High and low histological grade usingmLO image.

About the fractal dimension extracted from two projections (CC andmLO) of mammograms, there was not significant difference between the cohort mean (CC: mean ± std= 1.1583±0.067) (MLO: mean ±std =1.1551±0.055). For the high-grade differentiation, there was no statistically significant difference between CC andmLO images fractal dimension (*P* value=0.438 and 0.435). High grade fractal dimension mean were respectively 1.142±0.044 and 1.144±0.075 for CC andmLO images against 1.166±0.050 and 1.160±0.057 for low grade breast cancer Table 2.

Table 2. Fractal dimension of low- and high-grade breast cancer using CC andmLO images.

Fractal Dimension	Mean (±Std)		
	High Grade	Low Grade	*P*-value
CC Images	1.142(±0.044)	1.166(±0.050)	0.438
MLO Images	1.144(0.075)	1,160(±0.057)	0.435

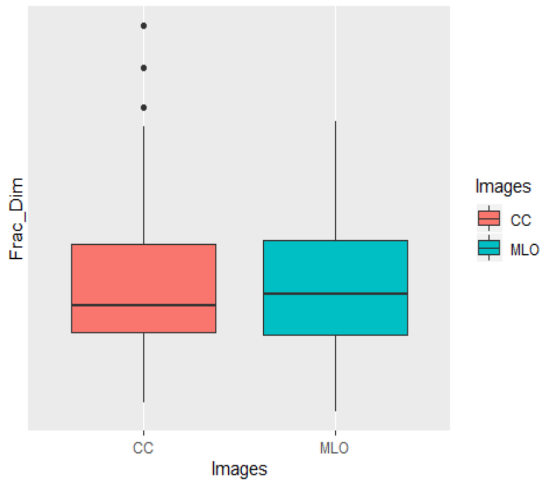

Fig. 2. CC andmLO fractal dimension distribution.

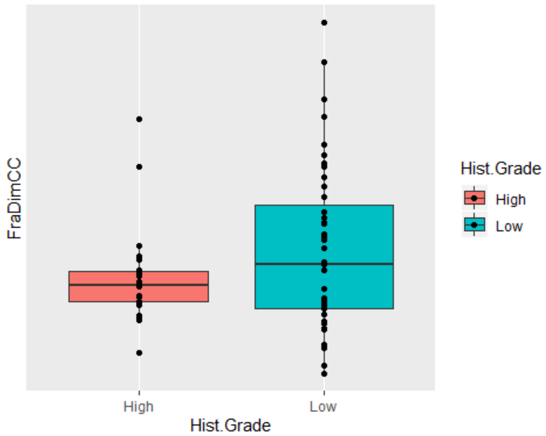

Fig. 3. histological high and low grade fractal dimension using CC images.

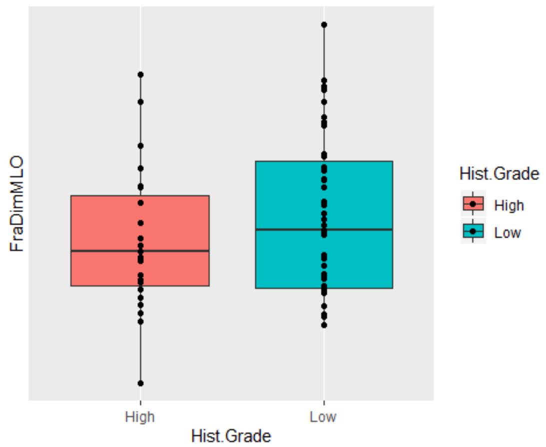

Fig. 4. histological high and low grade fractal dimension usingmLO images.

Discussion

Morphological analysis, in particular margin analysis of breast tumor on mammogram has contributed to a better characterization of its biology. It is well-known that high-grade breast cancers show circumscribed margins because of their high cellularity and rich hyaluronic acid extracelluar matrix and inflammatory host reaction, whereas low-grade cancers show a spiculated margin because of their low cellularity, rich collagen matrix and desmoplastic host reaction (Stavros *et al.* 1995; Stavros 2004). Also Shin *et al*, noticed that in their study high grade breast cancer had the round shape resulting in its rapid evolution and low-grade presented irregular shape with spicule because of its fairly development with stroma reaction (Shin *et al.* 2011). In our study, breast cancer with regular margin displayed fractal dimension low value than breast cancer with irregular margin. Our result were consistent to Rangayyan and Nguyen, who also reported that breast tumor with more irregular shape had higher fractal dimension value (Rangayyan and Nguyen 2007). We observed that high-grade breast cancer fractal dimensions were lower than low histological grade cancer, mainly using CC mammograms. This difference was not statistically significant, but it suggests that high-grade breast cancer presents more frequently regular margin than low grade.

It is important to underline our study's limitations. Manual segmentation does not allow to find with more accuracy breast cancer margin on all mammograms mainly of young subjects who have denser breast. Mammography is planar medical imaging modality leading the superposition of several glandular structures with breast tumor. These two realities contribute sometimes to the inaccessibility of the real breast cancer margin. The small size of our cohort is also a limitation.

In conclusion, in this study we used fractal dimension extracted from mammogram for differentiation of high histological grade breast cancer from low grade. We recorded a lower mean value of fractal dimension for high-grade breast cancer without statistically significant. This finding shows that the high-grade breast cancer tends to have a regular shape. A future large study will confirm our observations.

References

Abràmoff DMD, Magalhães Dr PJ, Ram Dr SJ. 2004. Image Processing with ImageJ **7.**

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians **68,** 394-424.

Elston CW, Ellis IO. 1991. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology **19,** 403-410.

Fan M, Liu Z, Xie S, Xu M, Wang S, Gao X, Li L. 2019. Integration of dynamic contrast-enhanced magnetic resonance imaging and T2-weighted imaging radiomic features by a canonical correlation analysis-based feature fusion method to predict histological grade in ductal breast carcinoma. Physics in Medicine & Biology **64,** 215001.

Gilchrist KW, Kalish L, Gould VE, Hirschl S, Imbriglia JE, Levy WM, Patchefsky AS, Penner DW, Pickren J, Roth JA, Schinella RA, Schwartz IS, Wheeler JE. 1985. Interobserver reproducibility of histopathological features in stage II breast cancer. *Breast* Cancer Research and Treatment **5,** 3-10.

Huang S, Franc BL, Harnish RJ, Liu G, Mitra D, Copeland TP, Arasu VA, Kornak J, Jones EF, Behr SC, Hylton NM, Price ER, Esserman L, Seo Y. 2018. Exploration of PET and MRI radiomic features for decoding breast cancer phenotypes and prognosis. NPJ Breast Cancer **4.**

Lamb PM, Perry NM, Vinnicombe SJ, Wells CA. 2000. Correlation Between Ultrasound Characteristics, Mammographic Findings and Histological Grade in Patients with Invasive Ductal Carcinoma of the Breast. Clinical Radiology **55,** 40-44.

Rakha EA, El-Sayed ME, Lee AHS, Elston CW, Grainge MJ, Hodi Z, Blamey RW, Ellis IO. 2008a. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology **26,** 3153-3158.

Rakha EA, El-Sayed ME, Powe DG, Green AR, Habashy H, Grainge MJ, Robertson JFR, Blamey R, Gee J, Nicholson RI, Lee AHS, Ellis IO. 2008b. Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. European Journal of Cancer (Oxford, England: 1990) **44.** 73-83.

Rangayyan RM, El-Faramawy NM, Desautels JE, Alim OA. 1997. Measures of acutance and shape for classification of breast tumors. IEEE transactions on medical imaging **16,** 799-810.

Rangayyan RM, Mudigonda NR, Desautels JEL. 2000. Boundary modelling and shape analysis methods for classification of mammographic masses. Medical and Biological Engineering and Computing **38,** 487-496.

Rangayyan RM, Nguyen TM. 2007. Fractal Analysis of Contours of Breast Masses in Mammograms. Journal of Digital Imaging **20,** 223-237.

Sanduleanu S, Woodruff HC, Jong EEC, de, Timmeren JE, van, Jochems A, Dubois L, Lambin P. 2018. Tracking tumor biology with radiomics: A systematic review utilizing a radiomics quality score. Radiotherapy and Oncology **127,** 349-360.

Schneider CA, Rasband WS, Eliceiri KW. 2012. NIH Image to ImageJ: 25 years of image analysis. Nature Methods **9,** 671-675.

Shin HJ, Kim HH, Huh MO, Kim MJ, Yi A, Kim H, Son BH, Ahn SH. 2011. Correlation between mammographic and sonographic findings and prognostic factors in patients with node-negative invasive breast cancer. The British Journal of Radiology **84,** 19-30.

Stavros AT. 2004. *Breast Ultrasound*. Lippincott Williams & Wilkins.

Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. 1995. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology **196,** 123-134.

Tamez-Peña J-G, Rodriguez-Rojas J-A, Gomez-Rueda H, Celaya-Padilla J-M, Rivera-Prieto R-A, Palacios-Corona R, Garza-Montemayor M, Cardona-Huerta S, Treviño V. 2018. Radiogenomics analysis identifies correlations of digital mammography with clinical molecular signatures in breast cancer. PLOS ONE **13,** e0193871.

Theissig F, Kunze KD, Haroske G, Meyer W. 1990. Histological Grading of Breast Cancer: Interobserver, Reproducibility and Prognostic Significance. Pathology - Research and Practice **186,** 732-736.

Trevino V. 2018. Breast Cancer Images & Segmentation - Correlation of Gene Expression Subtypes and Image Features.

WHO. 2006. Guidelines for management of breast cancer. World Health Organization, Regional Office for the Eastern Mediterranean, Cairo.