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Geometrical Evaluation of Cervical Cells. Fractal and Euclidean Diagnostic Methodology of Clinical Application

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Abstract

Background: The concomitant use of fractal and Euclidian measurements has led to the development of new methodologies of cell evaluation, including a diagnosis of cervical cells that set up differences between normality and various degrees of lesion, to carcinoma. **Aim:** To confirm the diagnostic capacity of the methodology based on fractal and Euclidian geometry for the mathematical diagnosis through a blind study of normal cells and with different types of lesion, as atypia of undetermined significance (ASCUS), low grade squamous intra-epithelial lesion (LGSIL) and high grade squamous intra-epithelial lesion (HGSIL). **Methods:** 100 cells of Papanicolaou tests were analyzed and divided into 4 groups according to conventional parameters: 25 normal, 25 ASCUS, 25 LGSIL and 25 HGSIL. By means of the Box-counting Fractal Space, we calculated the fractal dimension and occupying spaces of the border and surface in pixels of the cell nucleus and cytoplasm. The diagnostic parameters of the previously developed methodology were applied and compared with the conventional diagnosis, setting up sensibility, specificity, negative likelihood ratio and Kappa coefficient. **Results:** The values of the occupation of the border and surface of the cell nucleus and cytoplasm were consistent with the values found by the diagnostic methodology previously found. The subtraction of the nucleus and cytoplasm frontiers presented values between: 189 and 482 for normality; 159 and 432 for ASCUS; 126 to 401 for LGSIL and 39 to 122 for HGSIL. A sensitivity and specificity of 100%, and a

Kappa coefficient of 1 were obtained. **Conclusions:** The capacity of the methodology to diagnose quantitatively the different stages in the evolution of the cervical cells observed in Papanicolaou tests was confirmed, from normality to HGSIL.

Keywords

1. Introduction

The cervical cancer occupies the sixth place among the most frequent types of cancer in women worldwide, while it is the twelfth most frequent at a general level [1]. In 2008, about 290,000 new cases of cervical cancer were detected. This pathology was responsible of near 5% of all the new cases of cancer in women. Though there are vaccines available against the papilloma virus (PVH) that prevents infections for the serotypes 16 and 18, which presumably are responsible for about 70% to 75% of all cervical cancers [2] [3], some strategies as massive vaccination against PVH implemented by the countries with a higher incidence have not achieved the expected success, due to their high costs [4] [5] [6]. For this reason, the cervicovaginal cytology (CVC) continues to be the most used test for the early detection of cervicouterine cancer [7].

Following up the evaluation of the CVC makes possible the detection of cells with lesions that indicate the development of the disease. However, there is not a worldwide consensus for this evaluation; also, it has been shown that there are inter and intra observer reproducibility problems, since that evaluation is based on qualitative operator-dependent observations. Reproducibility problems are also evidenced in the simultaneous observation of several qualitative parameters including the size of the nucleus and the cytoplasm [8] [9] [10] [11].

Some studies that apply fractal methodologies to the study of neoplastic structures have been developed, and some analyses of mammograms [12] [13], to the cells of the oral mucosa [14], in bladder invasive cancer [15], and in ocular tissue [16], among others [17] [18] [19], have also been applied. Recently, applications of fractal geometry to the analysis of the nucleus and cytoplasm of cervical cells have been developed [20] [21], which permit to differentiate normality of Low Grade Squamous Intraepithelial Lesions (LGSIL) and High Grade Squamous Intraepithelial Lesions (HGSIL), determining, moreover, mathematical relations of the ASCUS cells (Squamous Atypia of Undetermined Significance) which associate them to an state of normality or lesion. These works gave origin to a diagnosis that simultaneously applies fractal and Euclidian measurements to the border and surface of the nucleus and cytoplasm in the generalized fractal space of Box Counting, which, in addition to providing an objective and reproducible diagnosis of these states, establishes some values associated to the

evolution between LGSIL and HGSIL [22]. Afterwards, a generalization was carried out, through which all possible clinically observable cell evolution paths from normality to cancer were established, providing an objective and reproducible evaluation of normality and lesion, as well as the evolution of these two states [23].

2. Materials and Methods

Definitions.

- Boundary of the object: When superimposing the grid of 2 pixels next to the defined objects (cytoplasm and nucleus), the number of squares which occupy the contours of the objects will be named the boundary of the object.
- Surface of the object: Number of pixels occupying the interior of each of the measured objects (cytoplasm and nucleus).
- Difference between boundaries: Subtraction between the boundaries of the cytoplasm and nucleus.
- Fractal: derived from Latin *fractus*, meaning broken or fractured.
- Fractal dimension: measure used to evaluate the irregularity of an object. For the wild fractals the Box-counting fractal dimension is usually used.
- Box-counting fractal dimension: See Equation (A1) [20], let N the number of squares occupied by the object measured with the partition grid K, and D the fractal dimension. For the measurements developed in the present work we used two grids of 2 and 4 side pixels.

$$D = Log_2 \frac{N\left(2^{-(K+1)}\right)}{N\left(2^{-K}\right)} \qquad \text{Equation (A1) [20]}$$

Procedure. Within the database of the *Insight group*, 100 cells were selected, obtained from Papanicolaou samples of cervical squamous epithelium; they were split into four groups according to the conventional clinical evaluation provided by an expert pathologist: 25 LGSIL, 25 HGSIL, 25 ASCUS, and 25 normal. The cytology samples of cervical squamous epithelium selected for the study came from patients whose ages ranged from 20 and 53 year old. The diagnoses established through the conventional method were masked, and those of the cytology samples extended on plate were photographed with a zoom of 100×. A representative cell of each sample was selected. Afterwards, the photographs of the cells were taken to an image editor.

Two geometrical objects were defined: cytoplasm and nucleus, and using previously defined software, their boundaries with the grid of 2 pixels of side and their surfaces with the number of pixels were measured (see definitions). The fractal dimension of Box-counting of the boundaries of the objects was also calculated, using two grids of 2 and 4 pixels of side, then the subtraction between the values of the border of the nucleus and cytoplasm was also calculated. Once these measurements were found, they were analyzed with the mathematical parameters of diagnosis support of the previously developed methodology [23], where the values greater than or equal to 161 in the subtraction of the

cytoplasm-nucleus borders and nuclear surfaces less than or equal to 735 were associated to normality; values greater than 130 in the subtraction of the cytoplasm-nucleus border and nuclear surfaces greater than or equal to 972 were associated to LGSIL; while the HGSIL cells showed values lower than 120 in the subtraction of the cytoplasm-nucleus border. Values among 120 - 130 in the subtraction of the cytoplasm-nucleus border corresponded to the evolution between LGSIL and HGSIL.

Statistical analysis. The cytopathological diagnoses of the samples were unmasked, which were taken as the Gold-standard, in order to develop the statistical analysis. The value of the True Positives (TP) was estimated, corresponding to the cells which both for the evaluation with the mathematical methodology, and for the conventional diagnosis, were evaluated as sick people, the true negatives (TN) corresponding to the cells mathematically evaluated as normal, and equally with the conventional diagnosis, the false positives (FP) corresponding to the number of cells which are histologically diagnosed as normal, but mathematically as sick, and the false negatives (FN), which is the number of cells mathematically evaluated as normal but with a histological diagnosis of lesion. With these values, the sensibility and specificity, as well as the kappa coefficient were found. The cells classified as ASCUS, for not having a specific histological diagnosis of lesion or normality, were excluded from statistical analysis.

3. Results

The nucleus surface, measured in pixels, showed quantities between the following values: 301 to 714 for normality; 1277 to 4694 for ASCUS; 979 to 5431 for LGSIL and 573 to 2680 for HGSIL.

The nucleus frontier, evaluated in the grid of 2 pixel's side showed values among 37 to 55 for normal cells; between 74 and 134 for ASCUS; between 71 and 158 for LGSIL and between 65 and 188 for HGSIL.

The subtraction of the nucleus and cytoplasm frontiers presented values between: 189 and 482 for normality; 159 and 432 for ASCUS; 126 to 401 for LGSIL and 39 to 122 for HGSIL.

The fractal dimensions of the objects showed that these values cannot differentiate any state, confirming previous results.

When establishing the physical-mathematical diagnosis according to the results of Rodriguez *et al* [23], it was found that the diagnosis made by the pathologist for normal cells, LGSIL and HGSIL coincided with the mathematical diagnosis in all cases. Some examples of the values founded for each state can be seen at Tables 1-3.

Furthermore, cells conventionally diagnosed as ASCUS presented values of normal, LGSIL or evolution between LGSIL and HGSIL, which is consistent with previous findings. Examples of ASCUS mathematical diagnosis are shown at Table 4, where the cell No. 2 had values corresponding to normality; cells 1, 3, 4 and 5 had values corresponding to LGSIL, and cells 6 and 7 had values of evolution

Table 1. Measures of seven of the normal cells evaluated.

Cell No.	Nucleus Surface	Nucleus Frontier	Citoplasm Frontier	Subtraction of Cytoplasm-Nucleus Frontiers
1	378	40	361	321
2	644	37	226	189
3	510	46	398	352
4	505	55	531	476
5	714	41	490	449
6	483	48	530	482
7	301	52	287	235

Table 2. Measures of seven of the LGSIL cells evaluated.

Cell No.	Nucleus Surface	Nucleus Frontier	Citoplasm Frontier	Subtraction of Cytoplasm-Nucleus Frontiers
1	4601	158	461	303
2	2748	105	237	342
3	5431	135	340	205
4	1036	71	388	317
5	994	74	210	136
6	5377	141	521	380
7	979	110	511	401

Table 3. Measures of seven of the HGSIL cells evaluated.

Cell No.	Nucleus Surface	Nucleus Frontier	Citoplasm Frontier	Subtraction of Cytoplasm-Nucleus Frontiers
1	573	70	182	112
2	1658	111	155	44
3	599	65	153	88
4	2680	138	190	52
5	2203	249	203	46
6	1371	98	137	39
7	2592	170	99	71

Table 4. Measures of seven of the ASCUS cells evaluated.

Cell No.	Nucleus Surface	Nucleus Frontier	Citoplasm Frontier	Subtraction of Cytoplasm-Nucleus Frontiers
1	1395	134	495	361
2	707	87	394	307
3	4031	89	521	432
4	3504	166	528	362
5	2749	76	238	162
6	689	79	209	130
7	652	121	245	124

Table 5. Minimum (MN) and maximum (MX) fractal dimensions found in each group for the measured objects.

Diagnosis		Nucleus Measurement	Cytoplasm Measurement	Total Cell Measurement
NORMAL	MN	1.147	0.854	1.095
	MX	1.257	1.152	1.069
ASCUS	MN	1.109	1.219	1.135
	MX	0.874	1.223	1.284
LGSIL	MN	1.052	1.1	0.916
	MX	1.065	0.87	1.113
HGSIL	MN	1.044	1.206	0.806
	MX	1.291	1.29	1.308

between LGSIL and HGSIL.

Finally, Minimum (MN) and maximum (MX) fractal dimensions found in each group for the measured objects are presented in Table 5.

About statistical analysis, it was found that it was obtained a sensitivity and specificity of 100%; the negative likelihood ratio was zero, and Kappa coefficient was one.

4. Discussion

This work applies a mathematical diagnostic methodology based on fractal and euclidian geometry to 100 normal cells of the squamous cervical epithelium with diverse degrees of lesion, confirming the diagnostic capacity of the method through a blind study. The results evidenced that the measurements permit to determine objectively and reproductively the state of normality or of lesion, as well as the degree of evolution of the disorder. The significance of this study is that these findings allow using the method as a useful diagnostic tool at clinical level, overcoming the difficulties of reproducibility of the conventional methods of classification, such as the Bethesda system.

The developed measurements allow the differentiation between the ASCUS cells with lesion patterns or with patterns of normality, providing a useful objective diagnosis in decision making at clinical level, overcoming the difficulties posed by the ASCUS conventional diagnosis, to the extent that this diagnosis does not clearly show a state of normality or lesion.

Some previous studies have evidenced that though the specificity of the CVC is of 98%, its sensibility is around 51% [8]. On the other hand, the present study established values of sensibility and specificity of 100% for the mathematical test, a negative likelihood ration of zero, and a Kappa coefficient of one, evidencing the capacity of the fractal and Euclidian geometry used simultaneously to set up objective measurements of the state of normality or of lesion of the cell structure, independently from the analysis of the population or statistical type.

Previous studies had already made use of the fractal geometry to set up dif-

ferences between states of normality and cancer in different structures [12] [13] [14] [15]. For example, when a multifractal analysis of the connective tissue of interphase of the oral mucosa was carried out in different degrees of neoplasia lesion, spectrums of values for their discrimination were found, study carried out by Landini and Rippin [14]. Likewise, several findings have been identified in the field of statistical analysis of digital mammograms [12] [13]. Luzi *et al.* [15] analyzed, using statistical methods, the fractal dimensions of samples of bladder invasive cancer, resulting in the decrease of the fractal dimension with respect to the histological degree of lesion, what has been useful for the identification of the risk of cancer.

However, diverse research works have evidenced that the fractal dimensions analyzed in isolation not always lead to differential diagnostic information [24] [25] [26] [27], which has created the need for the development of mathematical concepts for the analysis. In the case of cervical cancer, the concepts of Cell Intrinsic Mathematical Harmony, and Variability of the Fractal Dimension were developed, which permitted the establishment of differences between normality and HGSIL, from fractal measurements of the nucleus, cytoplasm, and the whole cell [27] [28].

There was a recent development of a new method of evaluation of the erythrocyte structure based on fractal and Euclidian geometry simultaneously [29], and this led to the establishment of objective measurements of the border and surface of the cell structure, while considering its irregularity when applying these measurements in the generalized space of Box Counting. This innovation was used in the analysis of cervical cells, evidencing that values greater than the border of the nucleus are associated with states of greater gravity at histological level, allowing for a quantification of all the process of evolution from normality to cancer [30]. This finding constitutes the fundamentals of the diagnostic methodology evaluated in the present study [27], whose diagnostic applicability was confirmed. This method was also the basis for the development of a generalization through which all the possible paths of geometrical alteration of the cervical cells are established, from normality to HGSIL, constituting a useful method at diagnostic and preventive level [23].

The evaluation of the cell structure from the joint application of the fractal and Euclidian geometries makes possible the procurement of a better comprehension of the cell evolution phenomenon to carcinoma, since there is a geometrical generalization of the phenomenon in which the parts and the whole of the geometrical structure are determined, resulting in objective quantifying measurements of the state of normality or alteration for any particular cell of the cervix, without the need for epidemiological variables or statistical studies which account for population behaviors that sometimes are not applicable to each particular case [31].

Currently, it is not necessary to consider the causal determinism for the description of a phenomenon, since from modern physics, like statistical mechanics [32], and the chaos theory [33], causality has stopped being the ground for

the understanding of nature. From *Prigogine's chaotic-deterministic conception*, it is decreed that the order of the studied phenomenon is found from temporal windows of the phenomenon. In this way, upon the analysis of the cervical cell evolution from geometrical and mathematical measurements in this work, only temporary windows of cell evolution are obtained which are deprived of any causal relation, but that may have a temporary correspondence from a geometrical and mathematical acausal order. Expecting causes-consequences in molecular cascades or the influence of epigenetic factors in the evolution of cancer are appreciations which are not taken into consideration in the fundamental conceptualization of the completed process.

From the perspective of this acausal view of nature, and from ways of reasoning based on mental experiments, applications of physical and mathematical theories to different fields of medicine have been developed. In the case of cardiology, for example, the theories of probability and entropy contributed to the development of a diagnostic methodology whose clinical application has been demonstrated [34], and a geometrical law for chaotic dynamic systems has been found [35]; in epidemiology, predictions on malaria outbreak in Colombian towns were made in a three-week period of time [36]; in infectology, it was possible to predict the population of T CD4 lymphocytes from information reported in the blood picture [37], which turned to be of great importance for VIH patients; in molecular biology, a union predictive theory was developed, based on combinatory, probability and entropy logics applied to monomeric peptides presented by the class II HLA (Human leukocyte antigen) [38]. Recently, a new methodology for the prediction of mortality in Intensive care unit was developed, based on the analysis of hemodynamic variables with dynamical systems and set theory [39].

5. Ethical Aspects

The present research complies with the ethical principles of the Helsinki Declaration of the World Medical Association. According to Resolution 008430 of 1993, of the Ministry of Health in Colombia, the research is classified as risk-free, since physical calculations are carried out over results of reports and non-invasive tests of the clinical practice which have been previously prescribed, protecting the integrity and anonymity of the participants.

6. Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The participants signed the informed consent.

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Conflicts of Interest Statement

None declared.

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