Original Article

Ductal Carcinoma In Situ of The Breast: Modified Black Nuclear Grading System Revisited

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ABSTRACT

Background: This study aims to determine the pathologists' agreement of modified Black nuclear grading system and Holland classification applied to cases of ductal carcinoma *in situ* (DCIS).

Methods: Forty-three cases of breast lesions diagnosed as DCIS were selected to interobserver analysis. Eight pathologists received the same set of digitized images from microscopy of DCIS cases, and answered a questionnaire containing the criteria to compose the modified Black nuclear grade and Holland classification. In order to determine interobserver agreement and diagnostic accuracy, a web-based survey was created. It organizes the information collected from each participant pathologist providing the histological grading of the cases in both classification systems.

Result: Comparing the two classifications studied, there was a similar interobserver agreement among both schemes, showing Kappa value of 0.28 ± 0.02 for the modified Black nuclear grade and 0.32 ± 0.02 for the Holland classification. Hence the reliability for the applied to cases of DCIS was considered acceptable. The agreement among all pathologists and the gold standard pathologist similarly followed the results of the interobserver agreement, showing to be acceptable, with Kappa for de overall mode value 0.33 + 0.10 for modified Black nuclear grade and 0.55 ± 0.10 for Holland classification (p = 0.07). The findings of Kappa for the mode values among specialists in breast pathology and general pathologists were, respectively, 0.34 ± 0.11 (acceptable) and 0.26 ± 0.10 (acceptable) for the modified Black nuclear grade and 0.50 ± 0.10 (acceptable) and 0.26 ± 0.10 (acceptable) for Holland classification. Breast pathology specialists showed similar reproducibility for both evaluated classifications than pathologists not devoted to this subject.

Conclusion: The diagnostic accuracy was similar for modified Black nuclear grading system regarding Holland classification system.

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Introduction

The introduction of mammographic screening in the 1980s generated an explosive increase in the incidence of ductal carcinoma *in situ* (DCIS) by more than 500% from 1983 to 1992. Currently it represents approximately 30–40% of all mammographically detected breast cancers. Consequently this has led to an increased interest in the biology, classification, clinical behaviour, and treatment of DCIS[1,2,3,4] .

It has been estimated that if left untreated, DCIS will develop to invasive carcinoma in a significant proportion of cases, generally within 10 years of diagnosis. Clinical trials showed beneficial effect of lumpectomy especially with adjuvant radiation in cases of DCIS[5,6,7,8]. In some instances, DCIS may recur locally, and 50% recurs as invasive carcinomas[9,10,11]. Clearly, the most important determinant of recurrence is the adequacy of surgical excision, but pathological assessment of excision margins is beset with technical difficulties[12,13].

The DCIS is strictly defined as a proliferation of epithelial cells with malignant cytological and histological features within the terminal duct-lobular unit of the breast, confined within the basement membrane. DCIS is not a single morphological entity but a heterogeneous group of proliferative breast lesions with different malignant potentials that varies according to cytology and growth pattern. This reflects its clinical presentation, histopathology, radiologic features, expression of biological markers, and clinical behaviour[9,10,11]. DCIS classification has traditionally been based on growth pattern; a number of studies have shown a relation between this aspect and behaviour. Growth pattern, however, often varies from one part of the tumour to another, which at least partly explains why architectural classifications are associated with a low level of observer consistency[11-16].

Sub categorization of the ductal proliferations is far more difficult and has resulted in persistent interobserver variability among experienced pathologists, even when the same criteria are applied[17-23]. Cytonuclear, cytoarchitectural characteristics and patterns of necrosis were used to compose the different classification systems[12,20, 24,25].

The classification of Holland[24], used by the European Pathologists Working Group, emphasizes primarily cytonuclear differentiation and secondarily architectural differentiation (cellular polarization). This system classifies DCIS in three groups: poorly, moderately (intermediately), and well differentiated[24].

Black and colleagues[26,27] evaluated the prognostic significance of the tubule formation and the nuclear features separately and concluded that only nuclear morphology is a significant prognostic factor. They proposed a nuclear grading system with five grades. Contrary to common practice, grade 0 and 1 were used to designate the most poorly differentiated, or anaplastic neoplasms, whereas grade 4 reflected the well-differentiated tumors. This reversal of the numerical order remained a disturbing aspect of this nuclear grading system and contributed to a lack of wide support for its application. The nuclear-grading system of the Black and colleagues has been found to be useful in predicting prognosis[28].

Fisher and coworkers[29] devised a grading method and modified the Black nuclear grading system by reducing it from five to three grades after combining grades 0 and 1 into one group, and grades 3 and 4 into another. Furthermore, they inverted the numerical order so that grade 1 corresponded to the well differentiated carcinomas and grade 3 reflected the most poorly differentiated ones. There is no report in literature that has explored the issue of interobserver reproducibility and diagnostic accuracy according to the modified Black nuclear grading system. Table 1 shows the morphologic criteria for the two classification systems studied, as well as their graduation.

This study was performed to assess agreement, comparing interobserver results, and to determine the accuracy of the histological grade of modified Black nuclear grading system[29] and Holland classification[24] for DCIS, using a web-based program developed to facilitate the classification. Based on these findings, we identified, among the systems

TABLE 1: Morphologic criteria for each classification system analyzed in this study.

System	Nuclear grade	Cell polarization	Final DCIS grade
Holland (HL)	Well differentiated	Prominent	• Well differentiated
	Intermediately differentiated	Present, not prominent	• Intermediately differentiated
	Poorly differentiated	Absent/very focal	• Poorly differentiated
Modified Blacks Nuclear Grade (MBNG)	1	N/A	• Grade 1 (low grade)
	2		• Grade 2 (intermediate grade)
	3		• Grade 3 (high grade)

Note: N/A, no available

studied, the one with the highest degree of agreement and reliability. The factor of study was the analysis of DCIS classification systems comparing modified Black nuclear grading system[13] with Holland classification[25]. The outcome was the degree of interobserver agreement.

Materials and Methods

Slides of 43 cases of DCIS of the breast, diagnosed at "Hospital de Clínicas de Porto Alegre" (HCPA), Brazil, and at MD Anderson Cancer Center, USA, were chosen by convenience sampling. Typical examples of DCIS were considered to select these cases, as well as those where histological material was well processed. The slides selected were reviewed by two experts in breast pathology without knowledge of the clinical and demographic characteristics of patients. The cases were not selected based on ease of diagnosis, but because they represented different grades of tumor differentiation. Cases in which there was evident invasive ductal carcinoma associated or divergence between the original anatomopathological diagnosis and the review performed at selection were excluded. The case slides were stored at the HCPA Pathology Service and in the Pathology Department of University of Texas MD Anderson Cancer Center, and they were prepared from surgical specimens fixed in buffered formalin and placed in paraffin blocks, using 5µm thick sections stained with hematoxylin-eosin. The cases were presented in digital photographs, in JPEG format, to the pathologists participating in this study. The reviewing pathologists obtained several colored digital photomicrographs of the selected DCIS cases. The website created for this study provides images of the same field in three different magnifications (100, 200, and 400×). During analysis, the pathologist has the opportunity to enlarge each image provided. Each case had at least 5 images stored in JPG format, which the observers could access freely during the assessment with or without magnification.

A cross-sectional study was carried out to diagnose the grading of DCIS cases in order to assess the degree of agreement between pathologists in the city of Porto Alegre, Brazil. The privacy of all data obtained was ensured, and this information was used exclusively for the scientific purpose expressed in this research project, with a guarantee that the identity of participants would be kept confidential. This project was approved by the Ethics and Research Committee of the Graduate and Research Group (GPPG) at "Hospital de Clínicas de Porto Alegre".

Participating Pathologists

Pathologists who work in Porto Alegre hospitals with breast cancer services were invited to participate in this study. Among 35 pathologists invited by the researchers, 12 agreed to the terms of the letter of free and informed consent to participate in the study: 4 university lecturers, 4 medical assistants, and 4 medical residents. Three of them said that they were specialists in breast pathology. The invited participants, except for the medical residents, had the title of specialist in pathology, and were associated members of the Brazilian Society of Pathology. The medical residents were excluded for statistical analysis. All of them work at hospitals connected to centers of academic training. A pathologist specializing in breast pathology from the MD Anderson Cancer Center, USA (ER) was invited to act as gold standard.

Statistical Analysis

The Kappa statistical method was used to access interobserver variability and agreement of invited pathologists with the expert pathologist for diagnosis in each classification system. The Kappa (κ) values vary from 0 to 1, and 1 indicates perfect agreement. Lands and Koch suggest the following interpretation for different ranges of Kappa values: from 0 to 0.20 agreement equals poor or weak; from 0.21 to 0.40 agreement is acceptable; from 0.41 to 0.60 equals moderate; from 0.61 to 0.80 equals good; and from 0.81 to 1.00 equals excellent[30].

To evaluate the diagnostic agreement between pathologists, the value of κ was estimated for multiple categories and multiple observers. Statistical comparison of agreement between classifications was done using a comparison test between Kappa values for subgroups of pathologists using the formula from Svanholm et al.[31].

For each classification, the proportion of cases in which most pathologists agreed with the expert (gold standard) was also estimated. Moreover, the subgroups of pathologists were also evaluated by the mode value. Whenever there was a draw, it was assumed the higher grade one as the mode value. In order to estimate diagnostic accuracy, the value of Kappa was calculated for each pathologist and for the pathologist subgroups mode values. Program SPSS v.14.0 was used for statistical analysis of the data. According to the calculation, for a 0.7 Kappa, 95% confidence interval and 15% margin of error, at least 23 different cases of DCIS would be needed.

Result

None of the participants (experts and non-specialists) disagreed with the diagnosis of DCIS in the 43 cases evaluated. The eight pathologists perform their professional activities in hospitals linked to academic training centers. Three of the pathologists are experts in breast pathology. Five pathologists mentioned that they generally employ Van Nuys classification to grade intraductal lesions of the breast and one pathologist adopts Holland classification. All

participants confirmed that they had practiced pathology for more than 5 years. The expert pathologist defined as gold standard reports using modified Black classification for nuclear grade and Van Nuys in her routine to classify DCIS, and had practiced pathology between 7 and 15 years.

Table 2 shows the proportion of cases diagnosed for the two different classification schemes by the pathologist gold standard (the expert in breast pathology from the MD Anderson Cancer Center, USA).

Table 3 shows the proportion of diagnosed cases according to Holland classification and modified Black nuclear grading system by each of the 8 pathologists, separated by subgroups: breast pathology specialists and not experts in breast pathology.

The classification systems evaluated in this study presented acceptable interobserver agreement, as shown in Table 4. The classification systems of DCIS of the breast showed a similar overall diagnostic agreement and obtained Kappa index of 0.28 ± 0.02 for Black and 0.32 ± 0.02 for Holland.

Table 5 shows the degree of agreement between the pathologists and the gold standard pathologist (accuracy) for the two classification systems covered in this study.

For modified Black nuclear grading system, there was agreement among the 8 pathologists and the gold standard in 9 cases (20.93%). Taking experts into consideration, there was complete concordance with the gold standard in 20 cases (46.51%), 18 of those corresponding to high-grade DCIS and two cases corresponding to low and moderate. The accuracy for each pathologist was estimated with Kappa statistics, and ranged from 0.02 ± 0.08 to 0.63 ± 0.10, considered weak and good, respectively. The finding of Kappa values for the mode value representing all participating pathologists was 0.33 ± 0.10. For the experts in breast diseases Kappa values ranged from 0.18 ± 0.10 to 0.63 ± 0.10 (weak and good, respectively), and for the no specialists, from 0.02 to 0.49 (weak and moderate, respectively). Using the mode value, the Kappa value for experts was 0.34 ± 0.11(acceptable), while for no specialists it was 0.26 ± 0.10 (acceptable).

TABLE 2: DCIS cases classified in each histological grade in the two classification systems, by the gold standard reference pathologist.

	Grade3 Poorly differentiated n (%)	Grade 2 Intermediately differentiated n (%)	Grade 1 Well differentiated n (%)
Modified Blacks Nuclear Grading System (MBNGS)	21 (48.8)	10 (23.3)	12 (27.9)
Holland (HL)	24 (55.8)	10 (23.3)	9 (20.9)

TABLE 3: Distribution of histological grading scores of 43 DCIS cases evaluated by the 8 pathologists.

Type	Pathologist	Modified Black Nuclear Grade			Holland		
		Grade 3 n (%)	Grade 2 n (%)	Grade 1 n (%)	Poorly differ. n (%)	Interm. differ. n (%)	Well differ. n (%)
Pathologists specialized in breast disease	A	27 (62.8)	13 (30.2)	3 (7.0)	22 (51.2)	19 (44.1)	2 (4.7)
	B	28 (65.1)	13 (30.2)	2 (4.7)	33 (76.7)	6 (14.0)	4 (9.3)
	C	23 (53.5)	13 (30.2)	7 (16.3)	25 (58.0)	9 (21.0)	9 (21.0)
Pathologists no specialized in breast disease	D	27 (62.8)	8 (18.6)	8 (18.6)	25 (58.1)	11 (25.6)	7 (16.3)
	E	17 (39.5)	17 (39.5)	9 (21.0)	21 (48.8)	14 (32.6)	8 (18.6)
	F	33 (76.7)	8 (18.6)	2 (4.7)	27 (62.8)	14 (32.6)	2 (4.7)
	G	20 (46.5)	22 (51.2)	1 (2.3)	18 (41.9)	24 (55.8)	1 (2.3)
	H	27 (62.8)	15 (34.9)	1 (2.3)	20 (46.5)	23 (53.5)	0 (0.0)

TABLE 4: Degree of interobserver agreement of breast CDIS for the two systems studied.

	All participating pathologists n = 8 k ± SE	Pathologists specialized in breast disease n = 3 k ± SE
Modified Black Nuclear Grading System (MBNGS)	0.28 ± 0.02	0.43 ± 0.07
Holland (HL)	0.32 ± 0.02	0.38 ± 0.09

TABLE 5: Degree of agreement of the pathologists with the expert pathologist (gold standard) for the two classification systems studied

Type	Pathologists	Modified Black k ± EP	Holland k ± EP
Pathologists specialized in breast disease	A	0.38 ± 0.10	0.50 ± 0.10
	B	0.18 ± 0.10	0.37 ± 0.11
	C	0.63 ± 0.10	0.64 ± 0.10
	MODE	0.34 ± 0.11	0.50 ± 0.10
Pathologists no specialized in breast disease	D	0.49 ± 0.11	0.40 ± 0.11
	E	0.40 ± 0.11	0.47 ± 0.11
	F	0.02 ± 0.08	0.30 ± 0.10
	G	0.21 ± 0.10	0.19 ± 0.10
	H	0.27 ± 0.10	0.24 ± 0.10
	MODE	0.26 ± 0.10	0.26 ± 0.10
Total	MODE	0.33 ± 0.10	0.55 ± 0.10

p-values: 0.454 when comparing the mode for specialists with no specialists for MBNGS.
0.053 when comparing the mode for specialists with no specialists for HL.
0,070 when comparing MBNGS and HL for all groups of pathologists.

Considering the Holland classification, there was a complete agreement among the 8 pathologists and the expert in 8 cases (18.6%). The observed agreement between the pathologists and the gold standard pathologist had the test Kappa index ranging from 0.19 $\pm$ 0.10 to 0.64 $\pm$ 0.10, considered weak and good, respectively, corresponding to the Kappa index of 0.55 $\pm$ 0.10 for the mode value. As noted, the accuracy was better in the expert pathologists group, Kappa values ranged from 0.37 $\pm$ 0.11 to 0.64 $\pm$ 0.10, values considered acceptable and good, respectively. For the mode value, the experts had a Kappa index of 0.50 $\pm$ 0.10 (acceptable). In this group, there was complete concordance with the gold standard in 23 cases (53.49%), comprising 19 cases of DCIS poorly differentiated, 2 cases of intermediately differentiated and 2 cases of well differentiated.

Comparing the modified Black nuclear grade and the Holland classification there was no statistical significance difference between the Kappa of the mode for all groups of pathologists ($p = 0.070$).

Discussion

Several studies have examined the degree of agreement in DCIS classifications[17,21,23,32]. All of them varied in details, such as number of cases, origin of cases, divergence in the diagnosis of difficult cases, mode of exhibition of the cases, association with invading component, number of readings performed, pathologists origin and experience, and also whether there was some form of training prior to evaluating the cases. All the classification systems proposed consider primarily nuclear grade and necrosis, leaving the architectural pattern aside, or not taking it into account at all. The terminology of the classifications and the criteria used to compose them are different, but they share the recognition of three main subtypes of DCIS: high, intermediate, and low grade[4,11].

An ideal classification for DCIS should present a sort of characteristics. Firstly, it should be clinically useful, correlating the histological grade with the rate of local recurrence and progression to invasive carcinoma. Secondly, it should provide precise and unambiguous terms to define the characteristics of all different types of DCIS. Furthermore, it should be simple and easy to apply, even in cases with minimal DCIS compromised ducts. A high rate of agreement among pathologists is also important[7].

This study included 43 cases of DCIS selected by convenience sampling. The data analyzed were obtained through a standardized questionnaire on Internet containing the criteria to classify the cases of DCIS of the breast. The use of a computer program, created in our institution, makes the process of classification simpler and faster, since the program itself determines the final grade in each system studied. This model was also adopted to restrain the subjective description of the histopathological criteria evaluated. Likewise, the cases were presented in digitized images, allowing every pathologist to evaluate the same area of interest of the histological section in each case.

Even using this method that provides a more objective analysis, it was observed that the reproducibility remained low for the systems evaluated. Moreover, the use of digitized images may have impaired the evaluation of the number of mitoses, due to the lack of microscopic fields, so the pathologist had to estimate this information for each case. As the modified Black nuclear grade take into account the number of mitoses, it could have contributed to low degree of agreement shown in our study.

The comprehensive evaluation of five DCIS classifications by 23 European pathologists (the European Commission Working Group on Breast Screening Pathology) found that the inclusion of cell polarization, besides the nuclear grade, in reaching a final DCIS grade using Holland classification neither improved nor worsened the level of consistency that could be achieved by using nuclear grade only[21]. In the current study, the reproducibility of Holland classification and modified Black nuclear grading were similar, confirming that previous affirmative. However, there is still no evidence that any characteristic beyond nuclear grade and necrosis has prognostic significance.

Our study showed low interobserver agreement on the final histological grade for the Holland and modified Black nuclear grading system. Whenever participants were divided into subgroups according to their interest in breast pathology, greater agreement was found among those self-named breast specialists. This fact suggests that probably the criterion that has greater influence on pathologists' agreement is the appropriate training and the development of precise definitions.

The most important aspect that can be drawn from the current study is that the modified Black nuclear grading system showed the same interobserver reproducibility and accuracy than the classification of Holland for DCIS. Therefore, the modified Black nuclear system can be an alternative to classify DCIS breast lesions. Pathologists specialized in breast pathology showed greater reproducibility and accuracy for both classifications compared to the others subgroups. These findings lead us to conclude that the academic institutions of this city should introduce training and quality-control programs in order to improve the rates of diagnostic agreement.

There are a number of potential limitations in this study. First, it could be argued that our results may not be representative of the level of agreement attainable in general pathology practice because of the small numbers of participating pathologists. We must also consider the fact that the participants were volunteers who made themselves available to participate in this study. Second, the pathologists in this study were asked to render their diagnosis following examination of selected digital images rather than following examination of whole histological sections under the microscope, as it is done in routine clinical practice. However, given that the goal of this study was to assess observer agreement in the classification of specific lesions, we believe that the use of digital images could be regarded as a strength of the study as it required the participants to base their diagnosis solely on microscopic features of the lesions in question without the aid of surrounding histological cues.

Regardless, our results should be analyzed with some caution, because this is a study with a unique methodology, both in case presentations and in the determination of the histological grade, based on criteria of a standardized questionnaire.

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