Bahrain Medical Bulletin, Vol. 27, No. 4, December 2005

Ductal Carcinoma in Situ of the Breast; Review of Classification Schemes and Their Clinical Significance

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The increasing use of screening mammography over the past two decades has led to five-fold increase in the diagnosis of ductal carcinoma in situ (DCIS)[1]. Thus pathologists are being increasingly faced with the challenge of diagnosing cancer in its early stage. The challenge faced by pathologists today is not just to detect pre-invasive conditions but to be able to further classify them into the various subgroups that may potentially have different biological behaviors. The interest in this area was heightened after the widespread use of breast conservation therapy.

The aim of this review is to highlight this controversial area of pathology, clarify the existing classification schemes, emphasize the clinical significance of its different subtypes and identify the minimum required data to be recorded in any pathology report describing DCIS.

Key Words: Ductal carcinoma in situ, classification, intraepithelial carcinoma, breast, pathology.

Bahrain Med Bull 2005: 27(4):

INTRODUCTION

What is ductal carcinoma in situ?

DCIS is characterized by proliferation of cytologically malignant epithelial cells, confined within the basement membrane of the mammary ductal tree[1,2]. This definition only helps to define DCIS in relation to invasive carcinoma. This is the upper limit of diagnosis but the minimum criteria required to identify low grade or early DCIS and differentiate these lesions from atypical ductal hyperplasia (ADH) are still questionable.

On a routine Haematoxylin and Eosin (H&E) stained slide, the minimum requirement for the diagnosis of DCIS is complete involvement of one or more ductal cross

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sections by uniform population of cells, the aggregate cross diameter of which exceeds 2 mm. Lesions displaying partial involvement of duct cross sections of 2 mm or less in aggregate cross-sectional diameter qualify as ADH. It is worth noting that the size criterion only applies for non-necrotic, low-grade variants of DCIS[1].

DCIS is not a single entity. It is now considered as a heterogeneous group of lesions that differ in their growth pattern, histological, cytological features and biological potential. Therefore, the need arises for a classification system that takes into consideration clinical implications.

Histological Classification

Many classification systems have arisen throughout the past decades[3-6]**.** These mostly stress some features like nuclear grade, necrosis and architecture as of prime importance in the classification systems. Features that are not widely adopted but variably incorporated including the size of DCIS, nucleolar grade, cell size and pattern of microscopic calcification. Inclusion of other features like homogeneity or heterogeneity of nuclear grade, presence of coexisting ADH, whether the lesion is tumor forming or asymptomatic, the status of c-erbB-2 (Her-2-neu), ER, PR, p53, DNA ploidy and proliferation fraction is more controversial[3-5].

The above criteria present individually or in combination constitute various classification systems, some of which are complex and confusing, possibly with little relationship to biological or clinical behavior.

In this review, the most commonly used classification systems are discussed, namely:

1. Architectural Classification
2. Modified European Pathologists Scheme
3. Van Nuys Classification
4. Ductal intraepithelial Neoplasia (DIN) concept.

Their applicability, usefulness and relationship to biological potential are also highlighted.

I. Architectural Classification

This is the traditional method for classifying DCIS and is primarily based upon the growth pattern, architectural features, of the tumor as:

- Solid Pattern: This features tumor cells that fill and distend the involved ducts and lack significant necrosis, fenestrations, or papillae. The tumor cells may be large, medium, or small (Fig.1).

  Figure 1

- Comedo Pattern: Characterized by prominent necrosis in the center of the involved ducts. The necrotic material frequently becomes calcified; and this may be detected by mammography as linear, branching "casting"

calcifications. The tumor cells are large and show nuclear pleomorphism. Mitotic activity may be prominent (Fig. 2).

Figure 2

- Cribriform Pattern: Characterized by the formation of back-to-back glands without intervening stroma. The cells comprising this subtype are typically small to medium size and have relatively uniform hyperchromatic nuclei. Mitoses are infrequent and necrosis is limited to single cells or small cell clusters (Fig.3).

  Figure 3

- Papillary Pattern: This shows intraluminal projections of tumor cells that, in contrast to the micropapillary variant, demonstrate fibrovascular cores and thereby constitute true papillations.

  A variant of papillary DCIS, intracystic papillary carcinoma, is characterized by tumor cells that are primarily or exclusively present in a single cystically dilated space.

- Micropapillary Pattern: This features small tufts of cells that are oriented perpendicular to the basement membrane of the involved spaces and project into the lumina. The apical region of these small papillations is frequently broader than the base, imparting a club-shaped appearance. The micropapillae lack fibrovascular cores. The cells comprising this type of DCIS are usually small to medium in size, and the nuclei show diffuse hyperchromasia; mitoses are infrequent (Fig.4)[2].

  Figure 4

Other rarer but equally important architectural patterns include: signet cell, clinging, pure apocrine cell, cystic hypersecretory and neuroendocrine types.

There has been; however, a general tendency to get away from this system, since most of the above types lack clinical relevance. Moreover, in this system there are insufficient criteria for the different subgroups and the fact that within the same lesion there may be a mixture of different growth patterns[5].

Nevertheless, it is important to record DCIS architectural type in the pathology report for the following reasons:

1. Correlating pathological and radiological appearances: This is particularly helpful in comedo DCIS, where it can exhibit a characteristic linear or branching calcification pattern on mammography. Coarse calcifications are generally associated with high and intermediate grade DCIS and fine calcifications or lack of calcifications with low grade DCIS. Therefore, for the radiologists it is important to know the morphological type of DCIS for auditing purposes[7]. Granular microcalcifications; however, can also be formed by calcified secretions or mucin with cribriform spaces and non-comedo DCIS.

2. Improving diagnostic consistency**:** This is useful for correlation with previous excisions and auditing diagnostic consistency on the same biopsy by different pathologists or the same pathologist at two different points of time.

3. Assessing the likelihood of invasion**:** Certain types of DCIS, for example, comedo type are more likely than others to be associated with microinvasion or indeed frank invasion[8].

4. Determining the probability of recurrence after local excision**:** Comedo DCIS, for example, is known for its local recurrence than the other types[8].

II. Modified European Pathologists Scheme

This classification is recommended by the European Community Working Group on Breast Screening Pathology and the United Kingdom National Health Service Breast Screening Program (NHSBSP)[6]. Currently, this is the most accepted classification to be recorded in the pathology report of DCIS lesions. It is primarily based on nuclear grading with a three tiered system. Hence DCIS is divided into high, intermediate and low nuclear grade[4,9].

High nuclear grade DCIS: Composed of cells with pleomorphic, irregularly-spaced and usually large nuclei exhibiting marked variation in size, irregular nuclear contours, coarse chromatin and prominent nucleoli; and mitoses are frequent [9].

A variety of growth patterns can occur in high nuclear grade DCIS, the most frequent of which is solid with comedo-like necrosis, which frequently contains calcifications. Less commonly, solid growth pattern is seen without necrosis. This is usually seen confined to the nipple ducts in cases of Paget's disease. Micropapillary and cribriform patterns are also seen in this context, but unlike low nuclear grade DCIS, there is rarely any polarization of cells covering micropapillae or lining intercellular spaces[3].

Low nuclear grade DCIS: Composed of monomorphic, evenly spaced cells with roughly spherical, centrally placed nuclei and inconspicuous nucleoli. The nuclei are usually but not invariably, small. Mitoses are few and individual cell necrosis is rarely present.

The growth pattern is usually that of cribriform and micropapillary. There is usually polarization of cells covering the micropapillae or lining the intercellular lumina. Solid growth is a less frequent pattern. When the terminal duct lobular units (TDLUs) are involved, the process can be very difficult to differentiate from lobular carcinoma in situ. Features in favor of DCIS are greater cellular cohesion and lack of intracytoplasmic lumina. Occasionally, however there may be a combination of both lesions.

Intermediate nuclear grade DCIS: This includes cases where, the nuclei show mild to moderate pleomorphism, which is less than that seen in high grade DCIS but lack the monotony of the small cell type. There is also high nucleo-cytoplasmic ratio with one or two prominent nucleoli.

The growth pattern may be solid, cribriform or micropapillary and the cells usually exhibit some degree of polarization covering papillary processes or lining intercellular lumina although it is not as marked as in low nuclear grade DCIS.

Although architecture correlates to some extent with nuclear characteristics, it has been shown that nuclear grade is a better predictor of behavior than architecture. For example, studies have shown that local recurrence rate increases after excision alone in cases of higher nuclear grade with or without comedo type necrosis[3,10].

In addition, this scheme correlates well with the expression of biological markers, for example, higher nuclear grade is closely correlated with large cell size, increased grades of intraductal necrosis, HER2/neu gene amplification, increased HER2/neu protein expression, higher cellular proliferation fraction, increased protein p53 expression, and absence of estrogen and progesterone receptor expression[3].

Lower nuclear grade lesions, on the other hand are typically diploid, estrogen- and progesterone receptor-positive, have a low proliferative rate, and rarely (if ever) show abnormalities of the HER2/neu or p53 oncogenes.

Lesions categorized histologically as intermediate grade are also intermediate between the high grade and low-grade lesions with regard to the frequency of alterations in these biological markers.

Studies of biological markers in DCIS tend to support these divisions[2].

III. Van Nuys Classification

The Van Nuys Scheme represents a dichotomous classification, where the pathologist recognizes high nuclear grade versus other nuclear grades and decides upon the presence or absence of necrosis (Table 1). This scheme seems to have a high reproducibility as pathologists make one or two dichotomous choices rather than judging a spectrum of grades[11]. It is however dependant on the definition of necrosis, where it is not addressed very clearly. What is the minimum requirement for necrosis? Would occasional desquamated or individually necrotic cells constitute necrosis? Or should it be ignored? Additional work is required to arrive at a consensus definition of necrosis[6].

Table 1 Van Nuys DCIS Classification.

Group 1	Non-high grade, without necrosis
Group 2	Non-high grade, with necrosis
Group 3	High grade (with or without necrosis)

IV. The Concept of Ductal Intraepithelial Neoplasia (DIN), (newly proposed classification)

Tavassoli has proposed a classification system that bears in mind that all intraductal proliferations are a continuum and that pathologists have traditionally subdivided them into intraductal hyperplasia (IDH) without atypia, ADH and DCIS[12,13]. This classification proposes that all proliferations are a continuum to be referred to as ductal intraepithelial neoplasia (DIN) for the following reasons:

1. There is a considerable degree of inter-observer variation to distinguish ADH from DCIS.
2. It has been shown that molecular changes precede morphological changes (i.e ADH and some IDH show the same molecular changes detected in adjacent DCIS and invasive carcinoma).

Depending on the increasing cytological and architectural alterations, Intraductal proliferations are classified into DIN 1a, 1b, 1c, 2 and 3, as they all represent risk factors, albeit of different magnitude, for subsequent development of invasive carcinoma (Table 2). Note that this classification removes all emotional stress of using the term " cancer" in the treatment of the patient[13].

Table 2. Classification of Ductal Intraepithelial Neoplasia with its corresponding current designation.

DIN classification	Description	Current designation
1a	Usual type hyperplasia	Usual type hyperplasia
1b	ADH	ADH
1c	Extensive ADH Low grade DCIS	ADH DCIS, low nuclear grade.
2	Cribriform or micropapillary DCIS with necrosis or atypia.	DCIS, intermediate nuclear grade.
3	DCIS with significant cytological atypia with or without necrosis.	DCIS, high nuclear grade.

DIN, ductal intraepithelial neoplasia; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ. Modified from: Tavassoli FA. Ductal Carcinoma *In Situ*: Introduction of the Concept of Ductal Intraepithelial Neoplasia. Modern Pathology.Vol.11, No. 2, p140-154.

Is there any consensus agreement on the classification of DCIS?

In 1997, a consensus conference was convened in Philadelphia to reach agreement on the classification of DCIS. Although the panel did not endorse any single

classification system, they recommended that certain features be routinely documented in the pathology report for DCIS lesions, including nuclear grade, the presence of necrosis, cell polarization, and architectural pattern(s)[14].

What information should be conveyed in the surgical pathology report?

Regardless of what classification scheme is followed, the following are the minimum requirements to be recorded in the surgical pathology report:

- Architectural type.
- Nuclear grade of DCIS.
- Presence or absence of necrosis.
- Extent of DCIS.
- Status of the margin of excision.
- Presence or absence of microcalcifications.

What is the Van Nuys prognostic index for DCIS? And should one incorporate it in the pathology report?

The Van Nuys prognostic index for DCIS is estimated by allocating a score from 1 to 3 to each of the following: lesion size, margins and grade. An aggregate score (Van Nuys prognostic index) is then generated by the addition of these three separate category scores (Table 3). Based on this index treatment recommendations for DCIS are generated to favor breast conservation. A lesion with an index of 3-4 receives only local surgical excision; a score of 5-7 receives local surgical excision and radiation treatment; scores of 8-9 may receive local surgical excision and radiation treatment with the caveat that the recurrence rate may be as high as 40%[6,15,16]. In my opinion, the latter group should be offered simple total mastectomy after explaining to the patient the relatively high recurrence rate. Subsequently, Fisher et al (Cancer 1999) have shown in their National Surgical Adjuvant Breast carcinoma Project (NSABP) that even the low risk group actually benefit from adjuvant radiotherapy and suggested giving adjuvant radiotherapy to all such patients[8]. Therefore, stratifying the patients into three groups may not help in deciding whether to give or not to give adjuvant radiotherapy, rather it might merely help in predicting the likelihood of local recurrence[8,17]. In that regard, it could be incorporated in the surgical pathology report.

Table 3. The Van Nuys Classification and Prognostic Scoring Index for DCIS.

	Histological Findings	Score
Grade	*Low grade (non-high grade) nuclei, no necrosis *Low grade (non-high grade) nuclei, with necrosis. *High grade nuclei, with or without necrosis	1 2 3
Lesion size	< 1.5 cm 1.6-4.0cm >4.1cm	1 2 3
Margins	>1.0cm 0.1-0.9cm <0.1cm	1 2 3

Modified from: Purcell CA, Norris HJ.Intraductal Proliferation of the Breast: A Review of Histologic Criteria for Atypical Intraductal Hyperplasia and Ductal Carcinoma In Situ, Including Apocrine and Papillary lesions. Annals of Diagnostic Pathology, 1998 April,Vol 2, No 2 p 135-145.

CONCLUSION:

The relative merits of these various classification systems of DCIS with regard to their inter-observer reproducibility and clinical utility remain to be established. Ultimately, a classification system that includes both histologic features and molecular markers of biological behavior may be necessary to provide the most clinically meaningful information of DCIS lesions [2]. Until then, the most practical classification is the currently used one (Modified European Pathologists Scheme) where DCIS is stratified according to its nuclear grade, presence or absence of necrosis, with a note of the accompanying recommended features described above.

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