Ductal carcinoma in situ: Current concepts

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RESUMEN
El carcinoma ductal in situ incluye un grupo heterogéneo de lesiones con características, alteraciones genéticas, manifestación y comportamiento clínico diversos. Debido al mayor uso de la mastografía de vigilancia, la detección del carcinoma ductal in situ puro se ha incrementado de manera importante. Los criterios diagnósticos del carcinoma ductal in situ dependen del grado de atipia citológica, pero en general incluyen características citonucleares y arquitecturales, la clonaldad de la población celular y la extensión de la lesión. Se han propuesto diversos sistemas de clasificación del carcinoma ductal in situ a fin de predecir la recurrencia de la enfermedad después de la resección quirúrgica, y la mayor parte de los sistemas se basa principalmente en el grado nuclear y, en segundo lugar, en la polarización celular y en la ausencia o presencia de necrosis. Debido a que el estándar de atención actual es la remoción quirúrgica de la lesión, la evolución natural del carcinoma ductal in situ no puede observarse directamente y, en la actualidad, es escasamente entendida. Sin embargo, varias líneas de evidencia apoyan el punto de vista de que el carcinoma ductal in situ sirve como un precursor no obligado de carcinoma invasivo. Debido a su naturaleza típicamente localizada, se ha demostrado que el carcinoma ductal in situ es tratable, en la mayoría de los casos, con escisión sola, generalmente en conjunto con radioterapia coadyuvante, con tasas bajas de recurrencia local. El riesgo de recurrencia depende de las características de la paciente –como el antecedente familiar de cáncer de mama y la edad al momento del diagnóstico– y de los factores del tumor, que incluyen extensión de la enfermedad, el tipo histológico, el grado nuclear, la presencia o ausencia de comedonecrosis, el patrón arquitectural y el estado de los márgenes de resección. La baja morbilidad de la biopsia del ganglio linfático centinela impulsó el interés de usar esta biopsia en el manejo de pacientes con carcinoma ductal in situ; sin embargo, su uso rutinario en este marco es en la actualidad motivo de intenso debate. Nuestra capacidad de predecir el comportamiento biológico del carcinoma ductal in situ mejorará con el uso de nuevas técnicas moleculares para identificar los biomarcadores específicos, lo que permitirá el manejo óptimo de pacientes con carcinoma ductal in situ.

Palabras clave: carcinoma ductal in situ.

ABSTRACT
Ductal carcinoma in situ (DCIS) includes a heterogeneous group of lesions with diverse morphologic features, genetic alterations, presentation and clinical behavior. Following the increased use of screening mammography the detection of pure DCIS has dramatically increased. Diagnostic criteria for DCIS depend on the degree of cytologic atypia, but in general include cytonuclear and architectural features, clonality of the cell population and extent of the lesion. Numerous classification systems have been proposed for DCIS in order to predict disease recurrence after surgical resection, and most systems are based primarily on nuclear grade and secondarily on cell polarization and the absence or presence of necrosis. Since the current standard of care is surgical removal of the lesion, the natural history of DCIS cannot be directly observed and is currently poorly understood. However, several lines of evidence support the view that DCIS serves as a non-obligate precursor to invasive carcinoma. Due to its typically localized nature, DCIS was shown to be treatable in most cases with excision alone, usually in conjunction with adjuvant radiotherapy, with low rates of local recurrence. The risk of recurrence depends on both patient characteristics, such as family history of breast cancer and age at diagnosis, as well as on tumor factors including extent of disease, histological type, nuclear grade, presence of comedo-type necrosis, architectural pattern and the status of the resection margins. The advent of sentinel lymph node biopsy with its low morbidity prompted interest in its use in the management of patients with DCIS, however its routine use in this setting is currently a matter of intense debate. Our ability to predict the biologic behavior of DCIS will improve with the identification of specific biomarkers using new molecular techniques and will enable optimal management of patients with DCIS.

Key words: ductal carcinoma in situ.

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Ductal carcinoma in situ (DCIS) is defined as a clonal, neoplastic proliferation of epithelial cells with all the morphologic features of malignancy within the confines of the pre-existing ducts and lobules of the breast without invasion through the basement membrane. DCIS includes a heterogeneous group of lesions with diverse morphologic features, genetic alterations, extent, presentation and clinical behavior.

Before the introduction of widespread mammographic screening, most cases of pure DCIS were symptomatic, presenting with clinical findings of a palpable mass, nipple discharge or Paget’s disease of the nipple and represented 1-3% of breast malignancies.1-4 Following the increased use of screening mammography, the detection of pure DCIS has increased dramatically. At present, for women over 50 years of age, approximately 15-25% of all breast tumors diagnosed within mammographic screening programs are pure DCIS,2,5 usually detected by typical patterns of microcalcifications.4,6

Since the current standard of care is surgical removal of the lesion, the natural history of DCIS cannot be directly observed and is currently poorly understood.

HISTOLOGIC FEATURES AND CLASSIFICATION

Ductal carcinoma in situ is a heterogeneous entity, with a wide range of histological appearances including different architectural growth patterns, different nuclear morphology ranging from minimal to severe nuclear atypia, and the presence or absence of necrosis and calcification.

Diagnostic criteria for ductal carcinoma in situ depend, in part, on the degree of cytologic atypia, but in general include cytonuclear and architectural features, clonality of the cell population and extent of the lesion (Figure 1). Lesions showing high grade cytologic features are diagnosed as DCIS irrespective of the size and extent of the proliferation. High-grade DCIS is composed by a population of atypical cells with marked nuclear pleomorphism, arranged in variable architectural patterns, including micropapillary, solid and cribriform. Although comedo necrosis is often present, its presence is not obligatory for the diagnosis of high-grade DCIS.

The diagnosis of low grade DCIS is based on three components, including architectural pattern, cytology, and disease extent.7 The diagnosis and management of pre-invasive breast disease: ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) –current definitions and classification. Low-grade DCIS is defined by a proliferation of monomorphic cells with uniform-sized nuclei and rare mitotic figures growing in arcades, micropapillae, cribriform or solid patterns. Individual apoptotic cells or small foci of necrosis may be seen and associated calcification may be present, usually within inspissated secretions. The neoplastic proliferation should involve more than two separate duct spaces or be more than 2 mm in greatest extent.

There has been much controversy regarding the classification of ductal carcinoma in situ.8 Ideally, a classification system should be easy to use and understand, be reproducible among pathologists, correlate with radiological features and provide prognostic information for patient management. The traditional classification system for DCIS was based on architecture and growth pattern (i.e. solid, cribriform, micropapillary, papillary, comedo, etc.).9 However, this system is neither reproducible among pathologists (as DCIS often shows a number of different architectural patterns in any given case), nor predictive of biologic potential for disease recurrence after excision or progression to invasive disease.

Numerous updated classification systems have been proposed for DCIS, most of which are based primarily on nuclear grade and secondarily on cell polarization and the absence or presence of necrosis. Although these updated classification schemes are more predictive of disease recurrence after surgical resection,10,11 they do not predict biological potential for progression to invasive disease. Since nuclear grade is the single most important predictor of recurrence after surgical excision of ductal carcinoma in situ, it is the primary criterion in most classification systems. Guidelines for nuclear grading suggest grouping nuclei into three levels (Figure 2): low-grade nuclei are defined as small (1.5-2 times the size of red blood cells), show a monotonous appearance with finely dispersed chromatin, occasional nucleoli and rare mitotic figures. High-grade nuclei are larger (more than 2.5 times the size of red blood cells), pleomorphic with coarse chromatin, multiple and prominent nucleoli and frequent mitotic figures, including abnormal forms. Intermediate-grade nuclei are those that show features in between the above two categories. Secondary classification criteria include cell polarization and necrosis. Necrosis is an easily recognized pathologic
Figure 1. Summary of diagnostic criteria used for usual hyperplasia, atypical ductal hyperplasia and ductal carcinoma in situ.

Figure 2. Guidelines for nuclear grading of ductal carcinoma in situ suggests grouping of nuclei in three categories. Low-grade nuclei (A) are small, monotonous with finely dispersed chromatin, occasional nucleoli and rare mitotic figures. High-grade nuclei (C) are large and pleomorphic with coarse chromatin, multiple and prominent nucleoli and frequent mitotic figures. Intermediate-grade nuclei (B) are those that show features in between the above two categories. Color figures of this article appear in the appendix 4 of this issue.

There is increasing evidence that systems for classification based on nuclear grade and necrosis show good reproducibility among pathologists. Utilizing the above discussed features, the first of the updated classification models was introduced by Lagios et al. and was based on nuclear grade and necrosis, without reference to architectural pattern as a primary determinant, a modification added by Scott et al. in 1997. The Nottingham classification model proposed in 1994 was based primarily on necrosis and secondarily on architecture. The Holland classification is another model that is based on differentiation, and it includes a combination of nuclear grade and cell polarization introduced a novel classification system referred to as the Van Nuys Prognostic Index (VNPI). Similar to other systems, the VNPI aimed to predict the likelihood of tumor recurrence based on the size of ductal carcinoma in situ, nuclear grade, and presence or absence of necrosis. Importantly, in addition to these factors, the VNPI was the first to include the extent of tumor-free margin as a determinant of tumor recurrence and assigned points (1-3) based on tumor size, nuclear grade (with and without necrosis) and extent of tumor-free margins. Patients with the lowest scores were shown to have a low rate of recurrence even without radiotherapy, while patients with the highest scores had a high recurrence rate unless treated with mastectomy. A subsequent modification of this classification system has recently been proposed which also includes patient age as a prognostic factor and is referred to as the modified.
Currently, there is no universal agreement on the features of ductal carcinoma in situ that can predict disease recurrence after surgical excision or progression to invasive carcinoma. Two consensus conferences were held in an attempt to design an appropriate classification system for DCIS. While no system was endorsed, the panels agreed that the following features of DCIS should be documented in the pathology report: nuclear grade, presence or absence of necrosis, presence or absence of cell polarization, and architectural patterns. It was also recommended that the report should document the highest nuclear grade within the lesion, and additional data should include margin status, size of tumor, the presence or absence of associated calcifications and correlation with radiologic findings.

**DIFFERENTIAL DIAGNOSIS**

Low grade ductal carcinoma in situ needs to be distinguished from usual hyperplasia and atypical ductal hyperplasia (ADH). Distinguishing hyperplasia from neoplasia (ADH and DCIS) is based on identification of a clonal cell process, as recognized by uniformity of cytomorphology and immunophenotype, such as cytokeratin and hormone receptor expression. The diagnosis and management of pre-invasive breast disease: ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH) – current definitions and classification. While usual hyperplasia is morphologically and phenotypically heterogeneous, ADH and DCIS are homogeneous in cell type and marker expression (Figure 3).

Although traditionally the distinction between benign proliferative breast disease and neoplasia (carcinoma in situ) in intraductal epithelial proliferations of the breast was thought to be between atypical ductal hyperplasia (ADH) and low-grade ductal carcinoma in situ (ADH) – current definitions and classification. While usual hyperplasia is morphologically and phenotypically heterogeneous, ADH and DCIS are homogeneous in cell type and marker expression (Figure 3).

Atypical ductal hyperplasia (ADH) was initially described based on exclusion criteria as “a proliferative lesion that fulfills some but not all criteria for a diagnosis of low grade, non-comedo type DCIS”. Although diagnostic criteria have been updated and refined, the diagnosis still rests on the absence of all the features required for the diagnosis of low grade DCIS. In general, ADH is diagnosed if the cytornuclear and architectural features of low grade DCIS are present but occupy fewer than two separate duct spaces. In practice, these criteria essentially recognize the same lesions. Larger foci of proliferations (up to 4 mm) are also accepted as ADH if associated with a radial scar/com-
plex sclerosing lesion or a papilloma. On the other hand, intraductal proliferations with some but not all criteria for DCIS that are seen adjacent to developed DCIS lesions are thought to be part of the same clonal proliferation as the dominant focus of DCIS, and should not be therefore classified as ADH in surgical excision material. However, similar appearing foci in core needle biopsy material are diagnosed as ADH with the understanding that a more extensive lesion fulfilling criteria for low grade DCIS may be found on surgical excision.

In rare cases the differentiation of DCIS from in situ lobular neoplasia (lobular carcinoma in situ [LCIS] or atypical lobular hyperplasia [ALH]) may pose difficulties, however, it is important because of its therapeutic implications. This distinction is most difficult when solid pattern low grade DCIS involves the acini (termed “cancerization of lobules”) with little or no lobular distortion. In solid pattern DCIS the neoplastic cells in most cases, at least focally, form small secondary spaces or microacini with the surrounding cells polarized toward the small lumens (Figure 4). The cells of lobular neoplasia tend to be dyscohesive with rounded cytoplasm detached from one another, in contrast with the cohesive, sharply circumscribed, crisp cell membranes of DCIS. In contrast to DCIS, intracytoplasmic vacuoles are frequently present in LCIS. Diagnostic difficulty may occur in occasional cases when poor tissue fixation leads to the appearance of dyscohesive cells in solid pattern DCIS (Figure 4). E-cadherin immunostaining is helpful in most cases, with the cells of LCIS being negative and those of DCIS showing positive membrane staining (Figure 4).

Partial involvement by lobular neoplasia of benign lesions such as collagenous spherulosis and usual hyperplasia may mimic the appearance of cribriform spaces amongst a proliferation of uniform cells mimicking cribriform DCIS. The involvement of collagenous spherulosis may pose a particular challenge (Figure 5). Although at low power both cribriform DCIS and collagenous spherulosis involved by lobular neoplasia contain a uniform population of neoplastic cells and appear fenestrated, the lumens of collagenous spherulosis contain characteristic eosinophilic spherules composed of hyaline of fibrillar material as opposed to the lumens of cribriform DCIS which tend to be empty or contain necrotic material and calcifications in some cases. In addition, the spherules of collagenous spherulosis are lined by a layer of myoepithelial cells which can be highlighted by immunohistochemical stains for myoepithelial markers. Immunostains for E-cadherin are also useful in this situation.

Variant forms of LCIS, such as pleomorphic LCIS (PLCIS) and LCIS with comedo-type necrosis, can also present diagnostic difficulties (Figure 6). Since the cytologic features of PLCIS are similar to those of high grade DCIS, distinction may be particularly challenging if the proliferations form mass lesions and necrosis and calcifications are present. In addition, DCIS may occasionally appear dyscohesive due to either single cell necrosis and/or tissue fixation. Since all PLCIS cases reported to date have been negative for E-cadherin by IHC, immunohistochemical stains for this marker is useful in this distinction.

On occasion, LCIS and DCIS may coexist in the same breast and even in the same terminal duct lobular units...
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Figure 5. Lobular neoplasia involving collagenous spherulosis mimicking cirriform pattern ductal carcinoma in situ. Although the lesion contains a uniform population of neoplastic cells and appear fenestrated, the lumens of collagenous spherulosis contain a fibrillar material and are lined by a layer of myoepithelial cells.

When classic features of both lobular neoplasia and DCIS in distinct components of the lesions involving the same spaces are present, a diagnosis of in situ carcinoma, mixed ductal and lobular type can be rendered. The distinct ductal and lobular components of these mixed lesions can usually be highlighted by E-cadherin immunostaining. On the other hand, rare in situ carcinomas display features of both LCIS and DCIS making categorization difficult if not impossible on routine histology. Approximately two thirds of these lesions will show either absent or diffuse strong membrane E-cadherine reactivity supporting their classification as LCIS or DCIS, respectively. In about one third of these cases, however, the constituent cells show a mixture of E-cadherin negative and positive immunoreactivity, suggesting that they may represent cases of in situ carcinoma with a truly mixed ductal and lobular phenotype.

Ductal carcinoma in situ with microinvasion (DCISM) is defined as the extension of cancer cells beyond the basement membrane into the adjacent tissues, with no single focus larger than 1 mm in greatest dimension. Invasive tumor cells must be in non-specialized connective tissue. The incidence rate of DCISM among all breast cancer cases is 0.68%-2.4%, and DCISM is seen in approximately 14% of DCIS cases. The potential for DCISM should be suspected for DCIS tumors that are large, show high grade histologic features and contain necrosis.

On occasion, cancerization of lobules with associated sclerosis and distortion or involvement of complex scleros-
ing lesions and sclerosing adenosis by ductal carcinoma \textit{in situ} may mimic invasive carcinoma (Figure 8). Correct diagnosis is mainly based on the recognition of the underlying architecture of these benign proliferations, although demonstration of the maintenance of a myoepithelial cell layer by immunohistochemistry (p63, smooth muscle myosin heavy chain, calponin) can be useful in difficult cases.

Ductal carcinoma \textit{in situ} with a cribriform pattern must be distinguished from invasive cribriform carcinoma, especially if scarring and distortion are present. Besides the irregular shape and varying size of the nests and the presence of a desmoplastic stromal reaction in invasive cribriform carcinoma, infiltration of tumor cells nests within adipose tissue or beyond the confines of lobular units may signify an invasive process. In addition, in invasive cribriform carcinoma the tumor cell islands lack a myoepithelial cell layer.

Ductal carcinoma \textit{in situ} (DCIS) with a papillary growth pattern should be distinguished from encapsulated papillary carcinoma and invasive papillary carcinoma. Papillary DCIS is characterized by the loss of myoepithelial cells within the proliferation (in contrast to benign papillomas), but retains a myoepithelial layer at the periphery of the involved duct spaces. In contrast, encapsulated papillary carcinoma shows loss of myoepithelial cells both within and at the periphery of the lesion and is considered by many as an invasive but indolent lesion.  

**BIOMARKERS AND MOLECULAR PATHOLOGY**

Many studies have evaluated the significance of biomarker expression in ductal carcinoma \textit{in situ} (DCIS). Estrogen receptor (ER) expression was demonstrated in 50% to 75% of DCIS lesions,\textsuperscript{45,46} most studies did not identify hormone receptor status as a clinically meaningful prognostic factor in DCIS.\textsuperscript{47,48} An exception is the study by Provenzano et al.,\textsuperscript{49} who concluded that negative hormone receptor and positive HER2 status were independent predictors of DCIS recurrence after adjustment for tumor grade. Currently the most important clinical implication of hormone receptor status in patients with DCIS is the resulting role for adjuvant hormone therapy.

HER2 is amplified and overexpressed in 32% to 55% of DCIS lesions in general, and it was shown to be more common in high grade (60-70%) compared to low grade (20%) lesions.\textsuperscript{50} In addition, HER2 overexpression in DCIS was shown to correlate with the presence of comedo-type necrosis and p53 accumulation, and inversely related to hormone receptor and Bcl-2 expression.\textsuperscript{51-54} Despite these findings, HER2 overexpression and gene amplification were not shown to be a prognostic factor in DCIS independent of standard histopathologic parameters. Mutations in p53 have been shown to correlate significantly with nuclear grade, presence of necrosis, and mitotic rate in multiple studies and is observed in approximately 25% of all DCIS lesions.\textsuperscript{55-59}

Recent molecular studies using comparative genomic hybridization (cGH) suggest that there may be at least two broad groups of DCIS lesions, characterized in part by loss or gain of chromosomal material at specific loci.\textsuperscript{18,60-62} There is a low grade group that is commonly ER-posi-

\textbf{Figure 8.} Ductal carcinoma \textit{in situ} involving the distorted spaces of sclerosing adenosis may mimic invasive carcinoma. Recognition of the maintenance of a lobulocentric architecture in sclerosing adenosis at low power and the presence of myoepithelial cells are clues to the correct diagnosis.
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The DCIS and invasive components of the lesions (either when concurrently present or in the recurrent setting) most often share similar morphological appearances and similar immunohistochemical and genetic profiles, supporting their origin from the same cell clone.61,77-80 Other studies of DCIS and invasive breast carcinomas has demonstrated that both show similar genetic profiles, when matched by histological grade and ER status,61,79,81 providing strong evidence that DCIS is a non-obligate precursor of invasive breast cancer. However, these studies have failed to reveal specific genetic alterations in breast carcinomas that are associated only with the invasive component and hence driving progression from the in situ to the invasive stage.82

Epidemiological studies have reported similar risk factors for invasive and in situ breast cancer,83-86 also supporting a common etiologic pathway for DCIS and invasive carcinoma.

As a non-obligate precursor of invasive ductal carcinoma, DCIS contains tumor cells that are confined to the pre-existing ducts and lobules of the breast. Once the tumor cells acquire the ability to invade through the basement membrane into the surrounding stroma, they transform into invasive carcinoma cells and eventually gain the capacity to metastasize to distant organs. Two different models have been proposed to explain the development of invasive breast carcinoma and the place of ADH/DCIS in this process. The traditional, multistep or linear model of breast cancer development and progression, based on morphological studies, hypothesizes that invasive carcinoma develops after breast disease proceeds through sequential stages, from premalignant hyperplastic breast lesions without (usual hyperplasia) and with atypia (ADH and ALH), to carcinoma in situ (DCIS and LCIS), to invasive carcinoma.25,87-89 In this model, low grade DCIS progresses to high grade DCIS and then “dedifferentiates” to become invasive carcinoma. This model was supported by analogy with mouse mammary tumor models and by epidemiological studies, which showed that the risk of breast cancer increased with the rate of cell proliferation and atypia in breast biopsies. However, the relationship between benign proliferative lesions, neoplastic but preinvasive lesions, and invasive carcinoma remains unclear and recent molecular data increasingly contradict this linear view of tumor progression.78,81,89,90
Recent studies comparing the immunohistochemical and genetic characteristics of ductal carcinoma in situ (DCIS) with those of invasive carcinomas have identified shared changes between low grade DCIS and low grade invasive cancers, and similarly between high grade DCIS and high grade invasive cancers. CGH studies of chromosome deletion demonstrated that 65% of low grade tumors had lost the long arm of chromosome 16 compared with only 16% of high grade tumors. This finding supports the theory that low grade carcinomas do not progress to high grade tumors; rather, low-grade and high-grade DCIS progress independently in a parallel fashion, known as the “parallel model” of breast cancer progression. This second model implies “commitment” of a subtype of DCIS to a specific subtype of invasive carcinoma (high grade or low grade): low grade DCIS tends to progress to low grade, while high grade DCIS tends to progress to high grade invasive carcinoma. Besides studies of chromosomal alterations, this model is also supported by histologic data showing that in the progression of DCIS to invasive disease, the grade of DCIS consistently corresponds to the grade of the coexistent invasive cancer. Another study evaluating 300 patients with invasive breast cancer associated with DCIS in the same breast showed that the degree of differentiation of DCIS was correlated with the grade of the coexistent invasive cancer. Patients with invasive carcinoma in this series also showed the same genetic changes as patients with coexistent in situ and invasive lesions. Clearly, the two models described above may not be mutually exclusive. Nevertheless, there is currently no direct evidence that usual hyperplasia is a precursor to ADH/DCIS or invasive carcinoma, neither from epidemiological, nor from histopathological or molecular biological studies.

**TREATMENT AND PROGNOSIS**

The goal of treating ductal carcinoma in situ (DCIS) is to keep the risk of progression to invasive and metastatic disease at essentially zero, while avoiding overtreatment of patients with a non-invasive lesion. Serial subgross three dimensional studies have elegantly demonstrated that most DCIS lesions are unifocal, only one region of the breast is involved in the vast majority of cases, and the spread of disease within the ductal system is usually continuous and often extensive at the time of diagnosis, although there may be small gaps up to a few millimeters in size between foci of DCIS, also indicates that most malignant lesions exhibit a lobar distribution within the breast, meaning that the simultaneously or asynchronously appearing, sometimes multiple, in situ and invasive tumor foci belong to a single lobe in one breast.

The disease-specific survival for patients with pure DCIS, regardless of the method of local therapy, is high, ranging from 96% to 98% in most studies. Due to its usually localized nature, DCIS has been shown to be treatable in most cases with excision alone, usually in conjunction with adjuvant radiotherapy, with extremely low rates of local recurrence of both in situ and invasive carcinoma after excision. Without adjuvant radiotherapy, 16%-22% of patients will develop a recurrence after breast conserving surgery, and about half of them recur in the form of invasive disease. The addition of adjuvant radiotherapy reduces the risk of recurrence to approximately 7-9%.

The risk of recurrence depends on both patient characteristics, such as family history of breast cancer in a first degree relative and younger age at diagnosis, as well as on tumor factors including extent of disease, histological type, nuclear grade, presence of comedo-type necrosis, architectural pattern and the status of the resection margins. Several studies have demonstrated that high nuclear grade DCIS lesions are more likely to recur than low grade lesions following breast conserving surgery. However, the observed difference may also reflect the duration of follow-up, as studies with long-term follow-up show higher rates of recurrence in low-grade DCIS over time suggesting that recurrences do occur in these cases, albeit with a longer latency period. Although some immunohistochemical studies have shown a correlation between negative ER and positive HER2 status and increased risk of local recurrence, overall, established biologic and molecular markers for invasive breast carcinoma have not been proven useful in the management of DCIS.

It should be kept in mind that involvement of the resection margins is a major risk factor for local recurrence when the prognostic/predictive value of various clinicopathologic and biologic features of ductal carcinoma in situ are evaluated. The importance of margin assessment as the most crucial factor in the management of patients with DCIS comes from a series of different sources. For example, a large study of 469 patients with DCIS...
clearly demonstrated that adjuvant radiotherapy does not decrease the recurrence rate when the DCIS was excised with margins of 10 mm or more. Even among patients with margin widths of 1-10 mm, there was no statistically significant benefit from adjuvant radiotherapy, and a statistically significant benefit from postoperative radiation was only seen in patients with a margin width of less than 1 mm.

The management of the axilla in patients with DCIS has changed dramatically over the years. By definition, ductal carcinoma in situ (DCIS) is preinvasive disease and as such has no potential to metastasize. Therefore, axillary lymph node dissection is not recommended as a part of surgical therapy for this disease. However, the advent of sentinel lymph node (SLN) biopsy with its low morbidity prompted interest in its use in patients with DCIS who were considered to be at high risk for harboring an invasive component (high grade, large, palpable tumors or mammographic mass lesions). All studies examining the utility of SLN biopsy in patients with DCIS are small, retrospective series and its routine use in the management of patients with DCIS is currently a matter of intense debate. Nevertheless, sentinel lymph node biopsy should be considered in patients with DCIS (especially if high risk for the presence of invasion) when the surgical treatment of choice is mastectomy, because removal of the breast precludes the subsequent performance of sentinel lymph node biopsy if invasive carcinoma is found on histologic examination, and leaves the only choice of axillary lymph node dissection for evaluation of the axilla.

**SPECIMEN HANDLING AND REPORTING**

The College of American Pathologists has recently published detailed recommendations regarding the processing and reporting of breast specimens containing DCIS. The main goal is to macroscopically and microscopically examine the clinical or radiological lesion for which the surgery was performed in order to establish the diagnosis and determine relevant tumor features, such as size, extent, grade and margin status. The excised specimen should be oriented by the surgeon and it should be correlated with the specimen radiograph and/or additional radiologic studies; this is especially important in the cases of non-palpable lesions to identify the radiographic area of interest. The specimen should be inked to maintain orientation and permit the measurement of the distance of any focus of ductal carcinoma in situ (DCIS) from the resection margin. It is generally recommended that, when practical, the entire specimen should be submitted in a sequential fashion for histologic examination, especially in cases with a known diagnosis of DCIS to exclude the possibility of invasion, completely evaluate the margins, and to aid in determining disease extent. If this is not possible, at least the entire area of the targeted lesion and the appropriate margins should be examined microscopically; this approach may be complemented with radiographic examination of the tissue slices to identify the targeted lesion. It is also recommended that if DCIS, LCIS or atypical hyperplasia is identified, all remaining fibrous breast tissue should be processed and microscopically examined.

The size (extent) of ductal carcinoma in situ (DCIS) is an important factor in patient management and correlates with the likelihood of the presence of residual disease after re-excision, close or positive margins, local recurrence, and the possibility of missed areas of invasion. It is well known that mammographic assessment, usually based on the distribution of calcifications, frequently underestimates, and sometimes overestimates, the extent of DCIS. There are multiple methods available for the pathologist to estimate the extent of DCIS. If DCIS is present in only one block, the area involved can be determined from a single slide by measuring the largest distance between DCIS foci. In the serial sequential sampling technique the entire specimen is blocked out in such a way that the location of each block can be determined and the extent of DCIS can be calculated by using a diagram of the specimen, the thickness of the slices, and the location of the involved blocks. This is the recommended method for all excisions known or likely to harbor DCIS. In the non-sequential sampling method the number of blocks involved by DCIS is correlated with the extent of disease of up to 4 cm. By multiplying the number of blocks involved by DCIS by the approximate width of a tissue section (multiplying by 0.4 cm is recommended) the pathologist can estimate the extent of the lesion. However, this method may underestimate extent of disease if not all areas of DCIS are sampled.

It is recommended that the Pathology Report for surgical excision specimen for DCIS should include the grade of DCIS, the presence or absence of necrosis, the architectural pattern(s) of the lesion, the presence or absence
of calcifications (with correlation to the mammographic findings), estimation of the size/extent of the disease and the distance of DCIS from the surgical margins.

**CONCLUSIONS**

Despite the identification over the years of several key features of ductal carcinoma in situ (DCIS), our current classification systems are inadequate for predicting the risk of disease recurrence or progression to invasive carcinoma. Our ability to predict the biologic behavior of DCIS will improve with the identification of specific biomarkers using new molecular technologies, such as array-based CGH, gene expression profiling and proteomics, which have already been applied to the study of invasive and preinvasive breast lesions. An improved understanding of the pathogenesis and natural history of DCIS will allow identification of meaningful molecular prognostic markers, potential molecular therapeutic targets and enable optimal management of patients with DCIS.

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