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NON-INVASIVE BREAST CANCER DIAGNOSIS AND TREATMENT (ES HWANG, SECTION EDITOR)

Ductal Carcinoma In Situ—Pathological Considerations

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Abstract

Purpose of Review Mammographic screening and radiological surveillance for local management has led to an exponential increase in diagnosis of ductal carcinoma in situ (DCIS) with limited impact on breast cancer specific mortality. Since definitive diagnosis of DCIS requires histopathological examination increase in radiological surveillance has resulted in significant increase in breast biopsies. Pathological characteristics of DCIS include grade, necrosis, size, anatomy, margins of excision, estrogen, and progesterone receptor status, and these features are useful for both prognostication and prediction.

Recent Findings Differential diagnosis of DCIS extends from atypical ductal hyperplasia to micro-invasive carcinoma and increasingly pathologists recognize intraductal lesions at the borderline between atypical ductal hyperplasia and ductal carcinoma in situ. Clinicopathological characteristics of DCIS continue to be significant in prospective trials and have been integrated with predictive molecular tools.

Summary Since most cases of DCIS do not progress to invasive cancer multiple tools which include clinicopathologic and molecular signatures are in the process of development and validation for personalizing treatment strategies for patients. Ongoing clinical trials are testing whether DCIS with favorable clinicopathologic characteristics may avoid loco-regional therapy which typically includes breast conserving surgery and radiotherapy.

Keywords Ductal carcinoma in situ · Grade · Diagnosis · Borderline · Biomarkers

Introduction

Ductal carcinoma in situ (DCIS) is defined as a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and is characterized by subtle to marked cytological atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer [1]. DCIS simply means that the neoplastic proliferation of ductal cells is confined within the normal ductal-lobular anatomy of the breast, and the neoplastic process does not have metastatic potential. Rare incidence of metastatic disease and breast cancer-specific mortality reported with a diagnosis of DCIS is most likely due to a missed diagnosis of invasive carcinoma due to inadequate sampling or erroneous diagnosis [2].

This article is part of the Topical Collection on *Non-Invasive Breast Cancer Diagnosis and Treatment*

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Routine mammographic screening has increased the incidence of DCIS from 2–3% to 20–25% in the USA [3]. The American Cancer Society estimates of 62,930 cases of DCIS will be diagnosed in 2019 [4]. The natural history of DCIS was partly illustrated in a series in which the diagnosis of DCIS was missed on biopsy. Invasive carcinoma developed in the region with DCIS, suggesting that DCIS is a precursor lesion [5, 6]. It has been reported that < 1% patients with DCIS may progress to invasive carcinoma [7], and increased surveillance has had limited, if any impact on breast cancer-specific mortality. Observational studies and experimental approaches suggest that low grade DCIS progresses to well to moderately differentiated carcinoma and high grade DCIS progresses to poorly differentiated carcinoma [8].

In the modern era, the standard of care for DCIS includes loco-regional therapy in the form of breast conserving surgery (BCS) and radiation therapy (RT) followed by systemic anti-estrogen therapy for hormone receptor positive disease [9, 10–15].Evidence-based guidelines recommend sentinel lymph node assessment only in patients with DCIS undergoing mastectomy as pathological examination may reveal an invasive carcinoma and mastectomy precludes subsequent

sentinel lymph node mapping [16]. Pathological examination of sentinel lymph nodes shows that if tumor cells are present they are commonly isolated tumor cells or micrometastases although macrometastases can be rarely seen. A meta-analysis showed that most but not all of these cases have an invasive carcinoma [17]. Pathologists should be aware that biopsy procedures can rarely "displace" normal epithelial cells into the sentinel lymph nodes [18].

Clinical Presentation

The overwhelming majority of cases with DCIS (80–85%) are detected by radiographic screening. DCIS may clinically present as unilateral nipple discharge, palpable mass, and erosion of the nipple (Paget disease of the nipple). The most common mammographic correlate of DCIS on mammography is calcifications. The size of DCIS on pathological examination may not correlate with span of calcifications seen on mammography [19]. Non-mass enhancement with delayed peak enhancement on MRI screening may correlate with DCIS. Bilateral, synchronous breast cancer is noted in less than 10% patients with half the cases being DCIS. Metachronous contralateral DCIS is more common [20].

Tissue Diagnosis

A definitive diagnosis of the lesions detected by imaging is achieved by pathological examination of breast tissue. In most cases, the foci of calcifications, architectural distortion, or non-mass enhancement can be targeted by image guided core biopsy. Stereotactic vacuum-assisted biopsies use mammographic imaging to target the abnormality, and MRI guidance is used to perform vacuum-assisted biopsy of lesions seen only on MRI scans. 3-D stereotactic vacuum-assisted core biopsy uses 3-D mammography for targeting. Rarely, the radiographic lesion is not amenable to core biopsies, and an open excisional biopsy is necessary to make a diagnosis.

If calcifications are targeted by the core biopsy, the core biopsy specimen should be radiographed to ascertain that the calcifications are present in the core and were adequately sampled. Core biopsies should be submitted entirely for routine histological processing and multiple levels examined (Fig. 1). Histological processing and microscopic examination take 1–2 days, as a definitive diagnosis of DCIS may require diagnostic immunohistochemical stains. Frozen sections of core biopsies are inappropriate and can lead to loss of diagnostic tissue. Histopathological examination of breast core biopsies can be challenging, and many lesions can mimic DCIS or invasive carcinoma. Definitive excision following an initial core biopsy diagnosis of DCIS may reveal invasive carcinoma in 15–27% cases [21]. For consistent quality of pathological

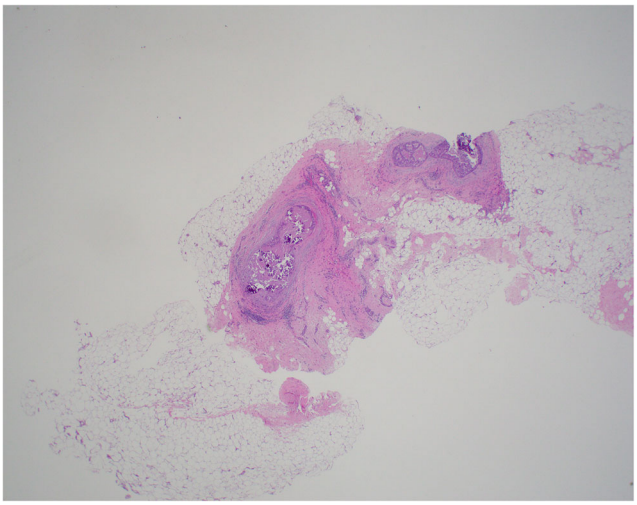

Fig. 1 A cylindrical piece of tissue from a vacuum-assisted core biopsy with ductal carcinoma in situ, high grade, comedo type with microcalcifications (2x)

diagnoses, it is good practice for more than one pathologist to review breast biopsies with a malignant or atypical diagnosis. This is especially useful in pathology departments that do not have a sub-specialized team of breast pathologists.

Fine needle aspiration (FNA), especially with image guidance, is a very useful technique but should be used judiciously for breast lesions. If the specimen contains neoplastic cells, the distinction between DCIS and invasive carcinoma cannot be made with certainty [22]; thus, FNA is not recommended for tissue diagnosis of mammographically detected microcalcifications [23]. FNA samples of DCIS may be less cellular and contain an admixture of neoplastic and benign epithelial cells. If a patient presents with nipple discharge, cytology of the nipple discharge fluid can be informative [24].

Open excisional biopsies are indicated when the lesion cannot be adequately sampled with image guidance. The lesion is usually localized prior to excision; the specimen should be handled as per American Society of Oncology/College of American Pathologists (ASCO/CAP) guidelines and oriented by the surgeon [25]. Specimens should be routinely X-rayed to ascertain that the lesion was excised and the entire specimen is best submitted for microscopic examination.

Gross Pathology

Historically the term "comedo" was first used to describe gross characteristics of breast tissue by Bloodgood in 1934 when he reported a case in which he assisted Dr. Halstead. "*The moment we cut into [the mass] and pressed on it, there extruded from its surface many grayish white, granular cylinders, which I called at the time comedos* [26]." It has been reported DCIS may form a radiographic mass in 10–40% cases [27]. The mass might be pre-existing due to underlying

fibrocystic change or may due to desmoplastic response to DCIS. In current practice, most cases with DCIS are detected by screening, and there is no gross correlate of DCIS in excisional biopsies. Typically gross examination of excision specimens with a prior core biopsy diagnosis of DCIS shows a healing biopsy site and fibrocystic change in the specimen.

Anatomy of DCIS

DCIS may be a contiguous process involving the ductal system, or there may discontiguous foci of DCIS involving different parts of the ductal system. Radiologic-pathologic studies have shown that most cases of DCIS are confined to a single segment of the ductal system; however, skipped areas can occur [19]. The anatomy of the excised specimen is also distorted spatially, as the spherical piece of excised tissue from a (pendulous) breast appears like a pancake ex vivo. The excision specimen is sampled in approximately 2-cm^2 pieces of tissue, which are processed and embedded in paraffin blocks. Since DCIS is diagnosed microscopically, the anatomy of DCIS must be ascertained by following careful grossing protocols and correlating gross examination with microscopic findings. This process is challenging because glass slides yield a two-dimensional picture, and DCIS is a complex three-dimensional process involving the ductal system.

Multifocality is commonly defined as discontiguous foci of DCIS confined to one quadrant of the breast. In the definitive NSABP B17 trial, multifocality was defined as "DCIS in two or more different blocks," and 60.8% cases in this trial were categorized as multifocal [12]. This definition has been widely used in the literature. Multicentricity has many definitions and refers to DCIS in multiple quadrants and thereby can be assessed only in mastectomy specimens and cannot be assessed in lumpectomy specimens [28]. The incidence of multicentricity may range from 0 to 75% depending on varying definitions, sampling protocols, and radiological screening methods. Hardman et al. reported multicentricity in 27% of cases [28]. With the increase in MRI screening, the incidence of multicentricity has increased [29]. Rauch et al. recently reported a series of 1657 patients with pure DCIS and defined multifocality as two or more foci of disease in the same breast quadrant within 5 cm of one another and multicentricity as DCIS in multiple breast quadrants or disease foci separated by more than 5 cm [30•]. In a multivariate analysis of this study, younger women with dense breast tissue were associated with multicentricity ($p < 0.0004$) and are more likely to undergo mastectomy ($p < 0.0001$).

As such, ascertaining the "size" of DCIS is inherently an inexact exercise; however, the span of DCIS in the excision specimen can be ascertained by careful mapping. The extent of DCIS is also reflected in the number of slides with DCIS and total number of slides from the specimen.

Protocols for Gross Pathology Evaluation

Intraoperative radiographic assessment of resection specimens is useful to evaluate adequacy of resection and relation of lesion/calcifications to the resection margin [31•]. The images are ideally reviewed by the multidisciplinary team, including surgeons, radiologists, and pathologists. Surgeons typically orient the specimen with two sutures, and the six aspects (medial, lateral, anterior, posterior, superior, inferior) of the specimen are inked with different colors. The ink can travel into normal crevices in breast tissue. This can make interpretation of inked margins difficult, and so this process may not identify margins correctly in a significant number of cases [32]. Shave margins are more accurate since the orientation is performed by the surgeon at the time of excision, and the true margin can be marked with one suture and inked accurately [33•]. Excision specimens with a prior diagnosis or radiographic suspicion of DCIS without a grossly identifiable lesion must be sampled more thoroughly than those with a well-defined invasive carcinoma. Sequential sampling of excision specimen allows for easy calculation of the span of DCIS and is recommended by CAP for all excision specimens with a prior diagnosis of DCIS [4]. Nonsequential sampling is inexact and may under or overestimate the extent of DCIS. The inked margins either from the excision or shaved specimens are best sampled perpendicularly. This allows accurate assessment of distance to margin. En face margins can overestimate the "positive" margin extent and lead to unnecessary re-excisions, and it is not feasible to assess distance to margin.

Microscopic Pathology

Ductal carcinoma in situ is definitively diagnosed by microscopic histopathological examination. In current practice, DCIS is classified by nuclear grade, architectural pattern, and presence or absence of necrosis and reported with current College of American Pathologists (CAP) protocols [4]. Many classification schemes have been proposed; however, none are included in the synoptic reporting standards developed by CAP [4, 34]. Grading of DCIS is currently based on nuclear features only, and DCIS is assigned into three grades: low, intermediate, or high. Architectural features are essential for diagnosis of DCIS, even though architecture is not used for grading. Not uncommonly, more than one grade of DCIS is seen in excision specimens, and the spectrum of grades should be noted in the pathology report. Intraluminal necrosis has been used extensively in classification schemes (comedo/non-comedo) with imprecise definitions of comedo necrosis [35•].

Diagnostic Criteria for DCIS

Intraductal proliferations include usual ductal hyperplasia(UDH), atypical ductal hyperplasia (ADH), and DCIS. The diagnosis of DCIS (Fig. 2) requires both architectural (rigid cellular bars; bulbous micropapillae; round, punched out spaces) and cellular features (cellular uniformity; even cell placement; distinct cell borders; no residual normally polarized cells) [1, 36]. In ADH, the atypical architectural and cytological features are seen in only part of involved ducts; therefore, the distinction between ADH and DCIS is inherently quantitative. The quantitative criteria for presence of DCIS are involvement of two membrane-bound spaces or size of at least > 2 mm [37, 38]. Nuclear grade assessment of DCIS may be challenging due to lack of diagnostic agreement between pathologists, especially for low grade DCIS. Onega et al. found agreement with 83% high grade DCIS but only 46% for low grade DCIS [39••]. In another study, there was a high level of concordance amongst pathologists for diagnosis of invasive carcinoma, but concordance was significantly lower for DCIS (84% (95% CI, 82–86%) were concordant, 3% (95% CI, 2–4%) were over interpreted, and 13% (95% CI, 12%–15%) were under interpreted) [40•].

Low Grade DCIS

DCIS populated by small, monomorphic cells typically with solid, cribriform, or micropapillary architecture is categorized as low grade. The nuclei show minimal variation in size and shape, have regular chromatin without nucleoli or chromocenters and rare if any mitoses (Fig. 3). Cellular necrosis may be present; however, central necrosis is rare. Psammomatous calcifications are associated with low grade DCIS. Low grade DCIS and lobular carcinoma in situ can be challenging to distinguish by histopathology alone, and immunohistochemical stains are useful to distinguish ductal from lobular differentiation. E-cadherin stain shows strong membranous staining in ductal cells and minimal staining in lobular cells, and p120 stain shows cytoplasmic staining in lobular cells and membranous staining in ductal cells [41].

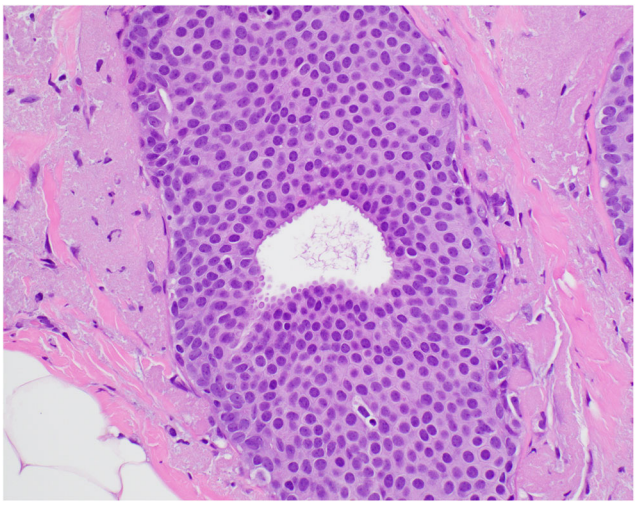

Fig. 3 Ductal carcinoma in situ, low nuclear grade composed of small, monomorphic cells (40x)

Intermediate Grade DCIS

DCIS populated by cells with mild to moderate pleomorphism, coarse chromatin, variably prominent nucleoli, and occasional mitoses is interpreted as intermediate grade (Fig. 4). Cellular or central necrosis and associated amorphous or psammomatous calcifications may be seen in intermediate grade DCIS.

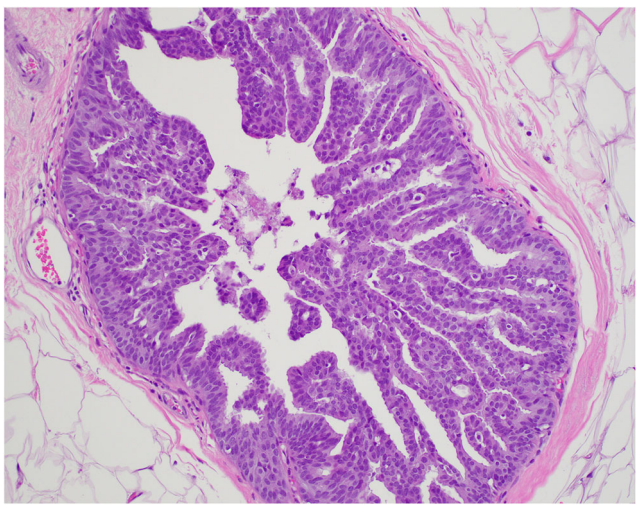

Fig. 2 Ductal carcinoma in situ with micropapillary and papillary architecture (10x)

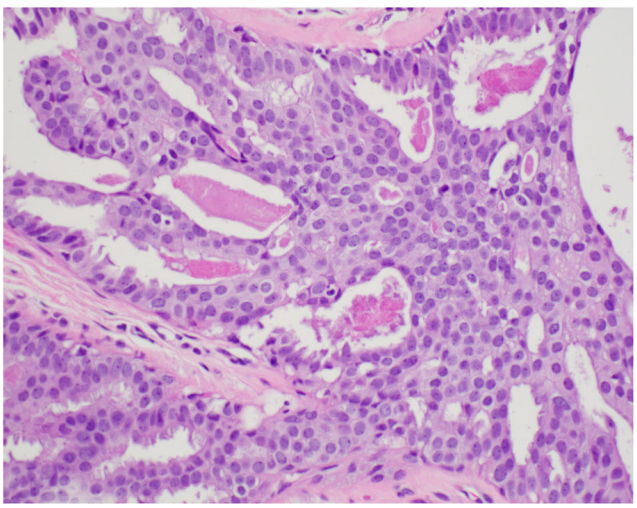

Fig. 4 Ductal carcinoma in situ, intermediate grade with mild to moderate pleomorphism with focal necrosis (40x)

High Grade DCIS

DCIS populated by very atypical cells with high pleomorphism, lack of polarity, coarse chromatin, prominent nucleoli, and frequent mitoses is categorized as high grade (Fig. 5). Central, expansile (comedo) necrosis with amorphous or coarse microcalcifications is commonly seen but is not necessary for diagnosis of high grade DCIS. A single duct with high grade nuclei is adequate for diagnosis.

Borderline Lesions Between Atypical Ductal Hyperplasia and Ductal Carcinoma In Situ

The distinction between ADH and low grade DCIS can be challenging for the practicing pathologist, and even breast pathology experts may have considerable inter-observer variability in diagnosis in lesions at the cusp of ADH and DCIS [42••, 43]. In a recent study, five expert breast pathologists attempted to classify a cohort of 105 borderline cases definitively as either ADH or DCIS. All five agreed in only 30% of cases [42••]. At a median follow-up of 37 months, 4 patients with majority diagnosis of ADH developed subsequent ipsilateral breast carcinoma (2 invasive, 2 DCIS). In this study, distinction between ADH and DCIS was not prognostic for risk of subsequent breast carcinoma.

From a practical standpoint, it is useful for the practicing pathologist and the multidisciplinary team to appreciate the category of borderline lesions between ADH and DCIS (Fig. 6). On a core biopsy, such lesions are best categorized as ADH, or a definitive diagnosis can be deferred to examination of the excision specimen. A diagnosis of borderline ADH/DCIS lesion on excision specimen should be made after peer review by more than one pathologist and more conservative therapeutic approaches considered.

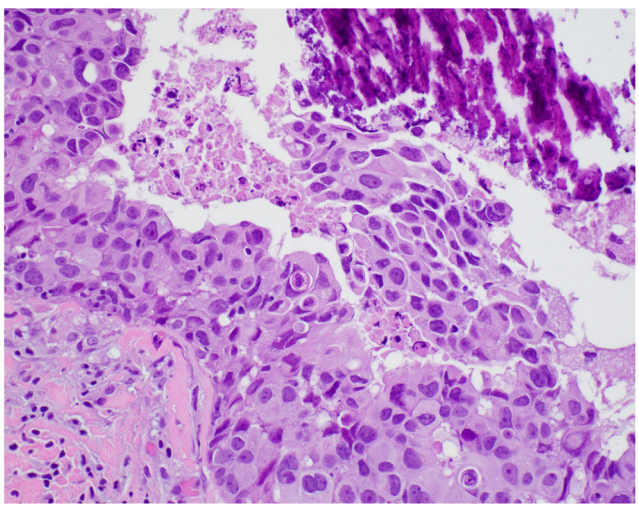

Fig. 5 Ductal carcinoma in situ, high grade with marked pleomorphism, central necrosis and coarse microcalcifications (40x)

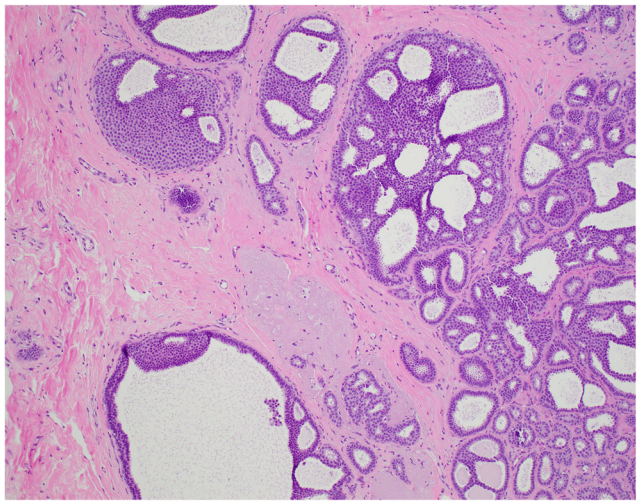

Fig. 6 Lesion with borderline features between atypical ductal hyperplasia and ductal carcinoma in situ (10x)

Margin Assessment

Consensus guidelines for margin assessment for DCIS undergoing BCS with whole breast irradiation were jointly published by Society of Surgical Oncology (SSO), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) and have been endorsed by a panel of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer [44, 45••].

The consensus panel used a meta-analysis from systematic review of 20 studies, including 7883 patients. Positive margin, defined as DCIS on ink, was associated with a two-fold increase in in-breast tumor recurrence (IBTR), which is not nullified with whole breast radiation. In NSABP B-17, cases with lumpectomy alone with positive margins had an IBTR rate of 8.1%, and those with negative margins had IBTR of 3.3%. In a meta-analysis by Marinovich et al., Bayesian analysis found patients with negative margins had lower rates of recurrence than those with positive margins (OR 0.45, 95% credible interval 0.30–0.62) [46•]. Frequentist analysis yielded similar findings, and the results persisted after adjustment for age, grade, RT, and endocrine therapy. These analyses showed significant decrease in IBTR for 2-mm margins compared to 0 or 1 mm and led to the choice of 2-mm threshold.

Based on this evidence, SSO-ASTRO guidelines qualify negative margins with a distance from the inked margin. Negative margins are defined as > 2 mm from ink, and based on the meta-analysis, more widely clear margins do not appear to enhance IBTR. Negative margin with DCIS < 2 mm from ink is not an absolute indication for re-excision, and the decision for re-excision is predicated on other prognostic features, e.g., extent and grade of DCIS, mammographic abnormalities, and age of patient. Havel et al. performed a meta-analysis of the impact of SSO-ASTRO guidelines and found a 35%

reduction in the odds of re-excision after guideline publication [47]. A randomized controlled trial to assess surgical and pathology techniques to sample margins in breast cancer demonstrated that cavity shave margins halved the rate of positive margins and re-excision undergoing BCS [33]. This definitive trial included 20% patients with DCIS (Stage 0).

Paget Disease of the Nipple

Sir James Paget described Paget disease of the nipple in 1874 [48]. WHO defines this entity as "a breast cancer characterized by the presence of malignant glandular epithelial cells (Paget cells) within the squamous epithelium of the nipple that may extend to into the areola and adjacent skin [49]." Paget disease of the nipple is usually associated with underlying breast cancer that may be invasive (53–60%) or DCIS (24–43%). Rarely Paget disease of the nipple arises in situ in the epidermis without underlying carcinoma [50, 51]. Microscopic examination shows large cells with abundant pale cytoplasm with pleomorphic nuclei in the epidermis (Fig. 7). Paget cells may be ER, PR positive and are usually positive for Her2 [52]. Prognosis and treatment depends on the underlying carcinoma.

Microinvasion

Microinvasion is defined by AJCC (8th Ed) as invasion measuring < 1 mm and is commonly seen in a background of DCIS and staged as T1*mic* [53]. Invasion irrespective of the size of the invasive carcinoma implies that the invasive cells have escaped from the normal anatomy through the basement membrane into the stroma and lack myoepithelial cells (Fig. 8). Prominent lympho-histiocytic reaction may be seen in foci of microinvasion.

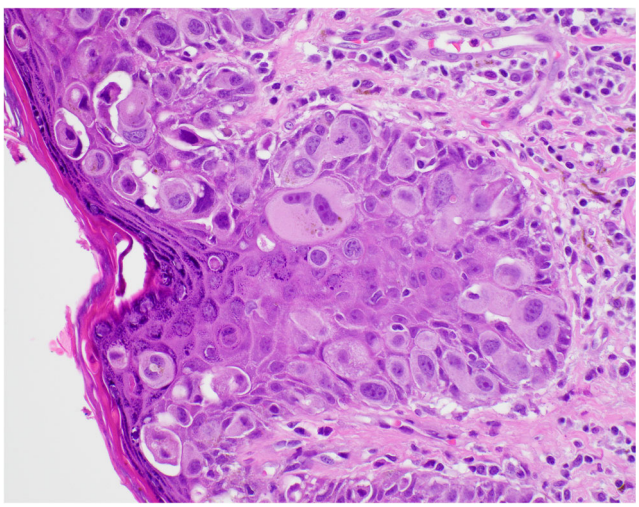

Fig. 7 Large atypical cells in the epidermis with abundant cytoplasm and pleomorphic nuclei with prominent nucleoli

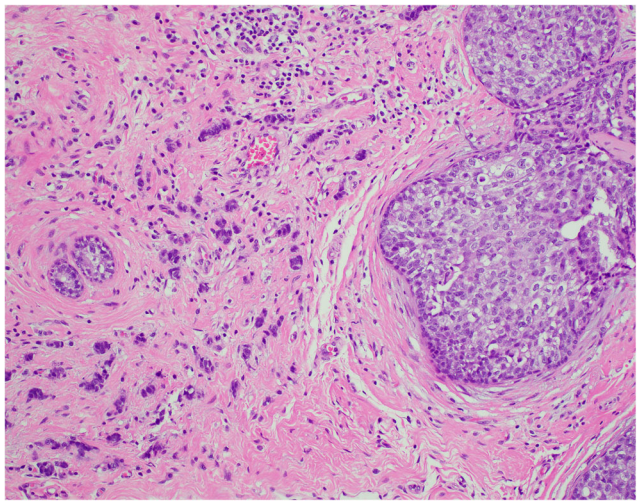

Fig. 8 Microinvasion in the vicinity of ductal carcinoma in situ (10x)

Immunohistochemical stains for myoepithelial cells (calponin, p63, SMA, SMM-HC) are very helpful diagnostically and show absence of myoepithelial cells in the invasive focus and presence in adjoining DCIS and normal terminal duct lobular units. Microinvasion is most often seen with high grade DCIS but can be seen with all grades and architectural patterns. Core biopsies can "displace" cells which can be mistaken for microinvasion, and displaced cells can also reach sentinel lymph nodes [18]. Displaced cells lack morphological and immunohistochemical characteristics of tumor cells and do not invoke a stromal response. In cases with extensive DCIS with multiple foci of microinvasion, there is no consensus as to how these cases should be staged.

Champion et al. studied a cohort of 134,569 cases of which 3.2% had microinvasion, 70.9% DCIS, and 25.9% with T1a invasive carcinoma [54•]. After adjusting for treatment, breast cancer-specific survival was significantly different between cases with microinvasion and the other two groups (DCIS: HR 0.59, CI 0.43–0.8; invasive: HR 1.43, CI 1.04–1.96); however, overall survival was better for patients with only DCIS and not significantly different between microinvasive and T1a disease (HR 0.83, CI 0.75–0.93). Sopik et al. interrogated the SEER database and reported that the 20-year actuarial breast cancer-specific mortality rate was similar for microinvasive carcinoma and small invasive carcinoma (0.2–1.0 cm) [55].

SSO-ASTRO guidelines recommend that DCIS with microinvasion should be considered to be DCIS when considering the optimal margin width. In contrast, margin assessment for cases with invasive carcinoma with focal DCIS should be done for invasive carcinoma as their outcome depends on the invasive carcinoma. Extensive DCIS close to many margins in multiple slides may be an indication for re-excision [56].

Prognostic and Predictive Clinicopathological Features and Biomarkers

Local recurrence and progression to invasive carcinoma has been linked to clinicopathological features such as young age, size, high grade, multifocality, and comedo necrosis. In a meta-analysis of randomized controlled trials and observational studies, tumor size, high grade, comedo necrosis, and multifocality were found to be associated with higher risk of ipsilateral recurrence [57, 58].

Various tools have been developed to assess risk of recurrence. USC/VNPI includes nuclear grade, necrosis, tumor size, margin width, and age. In a retrospective study with BCS with and without radiation, patients with a USC/VNPI low score treated with excision alone had < 6% local recurrence. In a second series of patients treated with mastectomy, all patients who recurred had a high score [59, 60]. Nevertheless, other investigators have not been able to replicate these results [61]. Shamilyan et al. studied Van Nuys classification as part of their meta-analysis and did not find a linear association between the score and recurrence, even though patients with higher scores had worse prognosis [57]. Another nomogram was developed by a group of investigators at MSKCC and includes age at diagnosis, family history, presentation, RT (after BCS), adjuvant endocrine therapy, nuclear grade, necrosis, margin status, number of excisions, and year of surgery [62]. This nomogram has been independently validated [63].

Estrogen (ER) and progesterone receptors (PR) are both prognostic and predictive markers for breast cancer. ER and PR are normally expressed in the breast glandular tissue and may be over expressed in neoplastic processes. A retrospective analysis of ER expression in NSABP B-24 suggested that tamoxifen benefit for risk reductions in ipsilateral and contralateral breast cancer following loco-regional therapy correlated with increased expression of ER [64, 65]. Level 1 evidence correlating level of expression and response to tamoxifen for DCIS is lacking. ER expression in DCIS mimics that seen in invasive carcinoma and 68.7% cases are positive for ER [66]. ASCO/CAP guidelines recommend assessment of ER and PR by immunohistochemistry for all cases with DCIS (Fig. 9) [25]. ASCO/CAP guidelines recommend that both percentage and intensity of staining should be reported and > 1% staining is categorized as positive.

Multiple ongoing clinical trials are testing anti-Her2 therapies in DCIS [67]; however, currently routine testing for Her2 is not indicated, and there are no standardized criteria to interpret and report Her2 staining. ER negativity, androgen receptor, Her2, p53, Cox-2 overexpression, and high proliferation assessed with Ki-67 have been associated with higher rates of local recurrence [68, 69, 70•, 71, 72]. The biomarker profile of DCIS typically mimics the profile of adjacent invasive carcinoma. Invasive breast cancer can be sub-typed by molecular analysis into four major categories: luminal A, luminal B, Her2, and basal like; these subtypes are also seen in DCIS [65, 73, 74].

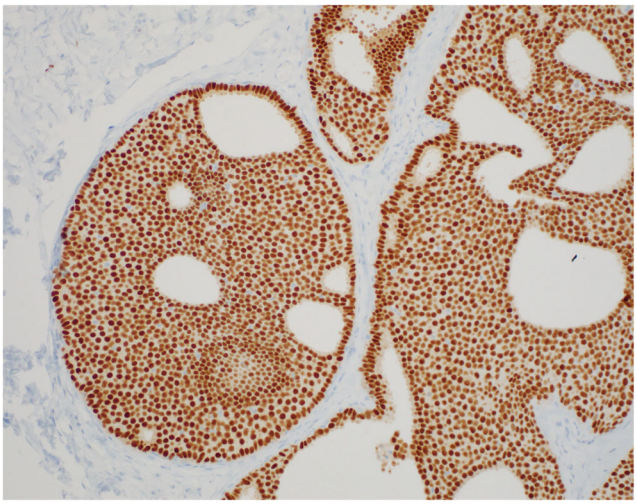

Fig. 9 Estrogen receptor nuclear stain in ductal carcinoma in situ (20x)

With the exponential increase in diagnosis of DCIS, there is a growing need to identify biomarkers that can categorize patients who do not need aggressive therapy and may avoid loco-regional therapy. Oncotype DX DCIS score is a commercially available prognostic score based on expression of 12 genes – seven cancer-related genes (Ki-67, STK15, survivin, CCNB1, MYBL2, PgR, and GSTM1) and five reference genes (ACTB, GAPDH, RPLPO, GUS, and TFRC). The DCIS score quantifies the 10-year risk of ipsilateral recurrence following diagnosis of DCIS without RT. The DCIS score was validated in a retrospective/prospective analysis of samples from ECOG E5194 trial of DCIS patients who underwent BCS with clear margins (>3 mm) and did not receive RT [75]. The continuous DCIS score was statistically significantly associated with the risk of developing recurrent DCIS when adjusted for tamoxifen use (prespecified primary analysis) and with invasive recurrence. DCIS score was also validated on a second (Ontario) cohort with a similar trial design, although negative margins were defined as no DCIS on ink [70•]. Multivariate analysis of both studies showed that age at diagnosis and size were significant predictors of recurrence in addition to DCIS score. DCIS score may be helpful in concert with other clinicopathological factors in identifying patients who can avoid RT.

Another tool which utilizes a combination of immunohistochemical assays (COX-2, FOXA1, HER2, Ki-67, SIAH2, PR, and p16/INK4A) and clinicopathological features (age, size, margin status, and palpability) yields a decision score that stratifies patients with DCIS into low-risk and elevated-risk groups [76•]. The score was validated in 526 DCIS patients treated with BCS and

RT. The score was significantly associated with ipsilateral and invasive recurrence and identified a Low and Elevated Risk Groups with 10-year risk of 4–7% and 15–23%, respectively. The Elevated Group received significant benefit from RT and no benefit in the Low Group.

Immune response to tumors has recently been successfully targeted by immunotherapy for many types of invasive tumors. An international working group has devised guidelines to assess tumor infiltrating lymphocytes (TILs) in DCIS [77]. Pruneri et al. reported that TILs were significantly associated with DCIS grade, age, comedo necrosis, and Her2 positive and triple negative subtypes; however, no association was found with ipsilateral recurrence [78]. In another observational study, subtypes of TILs (low numbers of activated CD8/HLA-DR positive, high numbers of non-activated CD8/HLA-DR positive, high CD115 positive macrophages) were associated with local and metastatic recurrences [79]. To date, there are no data to support any change in treatment based on TILs in DCIS, although studies are ongoing to evaluate the possible role of the immune environment in DCIS progression.

Conclusion

DCIS is a highly heterogeneous diagnosis, ranging from low volume, low grade, hormone receptor positive disease to extensive high grade, hormone receptor negative disease with very different prognostic, predictive, and therapeutic implications. Therefore, accurate assessment of grade, necrosis, anatomy, size, and margin status is essential for optimal patient care. Careful grossing and correlation with radiological studies is critical in determining the anatomy and margin status of DCIS. Since DCIS has both complex anatomy and biology a multidisciplinary approach for patient care helps to personalize therapeutic strategies. Predictive tools rely on a mix of clinical and pathologic criteria and help to personalize therapeutic options for patients with DCIS. Pathologists should be integral to multidisciplinary care of patients with DCIS and are encouraged to be conservative in diagnosis of DCIS, especially on core biopsies.

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Compliance with Ethical Standards

Conflict of Interest Baljit Singh reports past work as a consultant for Genomic Health Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
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