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Ductal carcinoma *in situ* with distorting sclerosis on core biopsy may be predictive of upstaging on excision

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Aims: The aim of this study was to examine clinicopathological features of patients with core biopsy diagnoses of ductal carcinoma *in situ* (DCIS) that may predict invasion on subsequent excision, as upstaging has significant implications regarding the need for axillary staging via sentinel lymph node biopsy (SLNB).
Methods and results: We identified 186 patients with a diagnosis of DCIS as the highest-stage lesion on core biopsy. Pathological and clinical features were assessed via slide and chart review, respectively. Distorting sclerosis was defined as irregular angulation of glands involved by DCIS but lacking definite invasion according to histology and/or immunohistochemical staining for myoepithelial markers. Thirty-two of 186 (17.2%) cases had upstaging to either microinvasive (nine) or invasive (23) ductal carcinoma. SLNB was performed in 29 of 32 (90.6%) cases with upstaging and in 55 of 154 (35.7%) cases without ($P < 0.0001$). Upstaging was significantly associated with the presurgical variables of radiological mass ($P = 0.009$) and distorting sclerosis ($P = 0.0005$) and the postsurgical feature of multifocality ($P < 0.0001$).
Conclusions: Sentinel lymph node biopsy is frequently performed for patients with upstaging from DCIS on core biopsy to microinvasive or invasive carcinoma on excision. DCIS with distorting sclerosis without definite invasion on core biopsy may be predictive of upstaging. This feature may be useful in selecting patients to undergo SLNB at the time of excision to avoid reoperation.

Keywords: breast, core biopsy, distorting sclerosis, ductal carcinoma *in situ*

Introduction

Percutaneous core biopsies of suspicious breast lesions have replaced excisional biopsies in many cases, because they are generally safer, more cost-effective, and less emotionally and physically disfiguring.[1] However, despite the advantages of minimally invasive biopsies, core biopsy is inherently limited in the amount of tissue obtained for pathological evaluation, resulting in the possibility of missing invasive disease and sampling only *in-situ* disease. On average, 6.6% and 22% of women diagnosed with ductal carcinoma *in situ* (DCIS) on core biopsy are upstaged to microinvasive and invasive ductal carcinoma, respectively, on subsequent excision, with an overall range of upstaging of 8–47%.[2–18] Several studies have investigated clinicopathological features in patients with core biopsy diagnoses of DCIS, in an attempt to predict invasion on subsequent excision, as this has significant implications regarding the need for axillary staging via sentinel lymph node biopsy (SLNB). Currently, SLNB is the standard practice in patients with invasive disease and clinically negative axillary lymph nodes. However, the use of SLNB in patients with DCIS on core biopsy is controversial. The American Society of Clinical Oncology recently published clinical practice guidelines on the use of SLNB for patients

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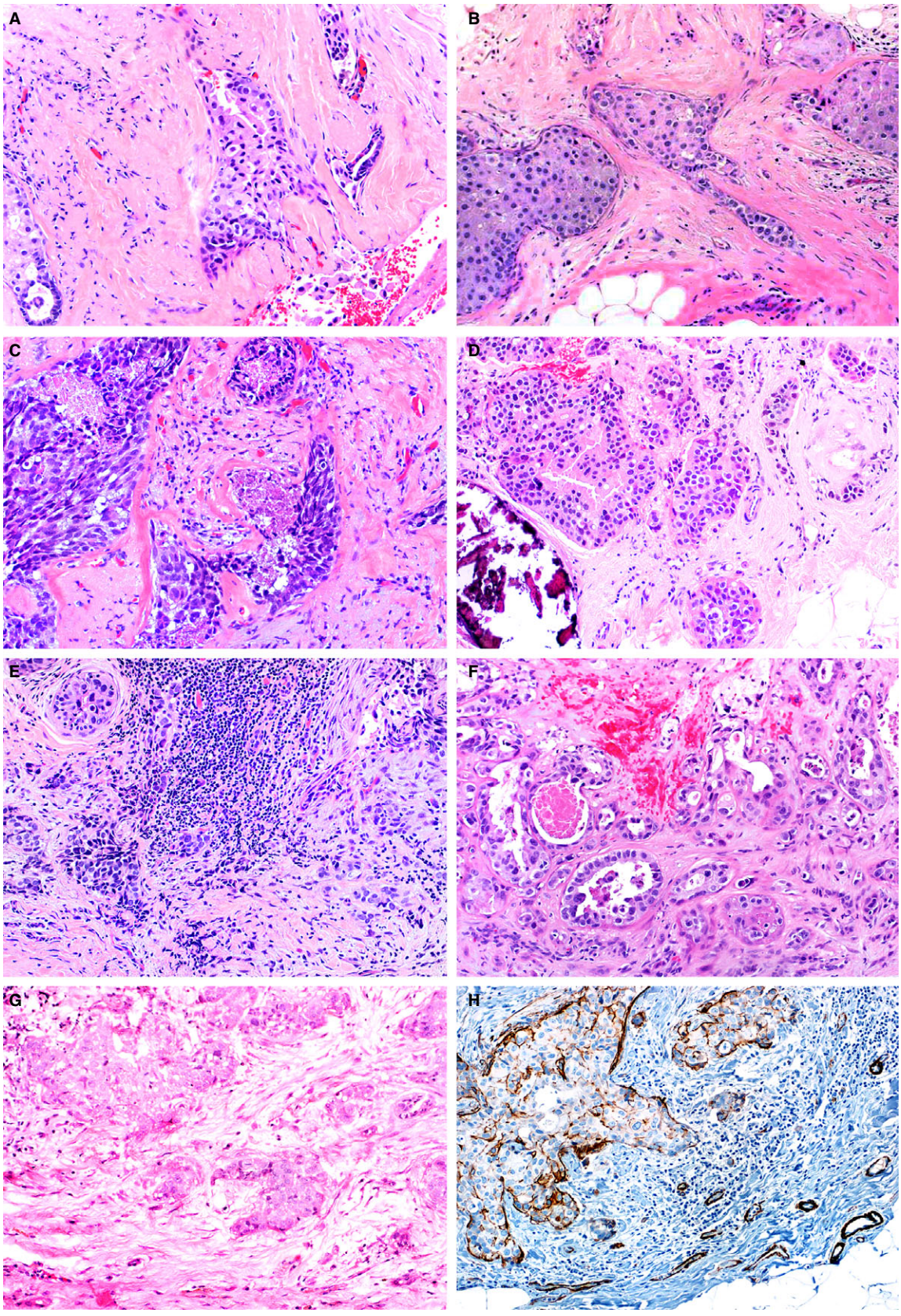
with early-stage breast cancer.[19] With regard to DCIS diagnosed by core biopsy, the panel recommends that women should be offered SLNB in the following circumstances: when a mastectomy will be the mode of definitive excision, as SLNB will not be technically feasible afterwards; when a mass highly suspicious for invasive carcinoma is either palpable or noted radiologically; or when the area of DCIS is ≥50 mm.[19] Because reoperation causes additional physical and emotional stress for the patient, is technically more challenging, and imposes additional financial burdens on the patient and healthcare system, SLNB should be performed at the time of excision if indicated. However, SLNB should not be performed in all cases of pure DCIS, owing to the low, but real, probability of complications, including allergic reaction to the dye used, lymphoedema, infection, seroma, longer duration of anaesthesia, and injury to regional nerves, resulting in sensory and motor deficits.[19] Ideally, patients showing features suggestive of invasive disease should be selected to undergo SLNB at the time of excision. To date, few features have consistently surfaced as strong predictors of upstaging on excision. The clinicopathological features that are most commonly associated with upstaging to invasive disease include the presence of a palpable or radiological mass, and core biopsy pathology of high nuclear grade DCIS with comedonecrosis.[3,5,6,13,15,17,18] In this study, we evaluated a combination of clinical and pathological features in core biopsies with DCIS in an attempt to determine novel features that may predict upstaging to invasive carcinoma on excision.

Materials and methods

After Institutional Review Board approval, a retrospective search (2006–2011) of the University of Michigan pathology electronic database identified 188 female patients with a diagnosis of DCIS as the highest-stage lesion on breast core biopsy. Only patients who underwent subsequent definitive excision (breast conservation therapy or mastectomy) at the University of Michigan were included. Core biopsies were either ultrasound-guided or stereotactic-guided vacuum-assisted core needle biopsies. Clinical characteristics including patient age, the presence of a radiological mass and/or radiological calcifications, biopsy method, number of sites biopsied, number of biopsy samples per site and timing of SLNB were obtained from patient electronic medical records. Diagnosis, size, multifocality (defined as two or more discrete foci at least 20 mm apart), the presence of calcifications in DCIS and the pathological status of sentinel lymph nodes [negative, micrometastasis (≤2 mm) and macrometastasis (>2 mm)] were obtained from pathology reports. All original haematoxylin and eosin-stained slides and available immunohistochemical (IHC) stains performed at the time of diagnosis were re-reviewed by two pathologists (J.P. and J.J.) with experience in breast pathology. Two cases with microinvasion confirmed by myoepithelial IHC staining were excluded. Histopathological features, including linear involvement of core biopsy, highest nuclear grade, presence of central necrosis, primary architectural pattern, cancerization of lobules, degree of periductal chronic inflammation, expression of oestrogen receptor (ER) and progesterone receptor (PR), presence of periductal fibrosis, and presence of distorting sclerosis, were included in the analysis. Focal was defined as involvement of one to three ducts, and extensive as involvement of more than three ducts. Distorting periductal sclerosis was defined as periglandular desmoplasia or fibrosis resulting in irregular angulation of glands involved by DCIS (Figure 1A–C), whereas periductal fibrosis was defined as a concentric rim of fibrosis encircling the duct without distortion of the lumen. Distorting sclerosis was defined as 'severe' when the distortion of the glands was marked and concerning for or difficult to discern from microinvasion via histological examination alone. Nuclear grade was determined according to consensus committee guidelines.[20] ER and PR immunostains were reviewed and categorized as positive (>10% staining), weak (1–10% staining), or negative (<1% staining). The primary architectural pattern of DCIS was categorized as solid, cribriform, comedo, micropapillary, papillary, or other.

All cases showing severe distorting sclerosis were further evaluated for invasion by IHC staining for myoepithelial markers (muscle-specific actin, clone HHF35, and p63, clone 4A4; Ventana, Tucson, AZ, USA) if not performed at the time of diagnosis. All cases showed intact myoepithelium, confirming the morphological interpretation of DCIS (Figure 1D).

Figure 1. **A–G**, Ductal carcinoma *in situ* (DCIS) with distorting sclerosis, with architectural distortion and irregular angulation of glands, and with 'severe' distortion in (**E**)–(**G**) (haematoxylin and eosin). **H**, Muscle-specific actin immunohistochemical staining highlights the myoepithelial cells in (**G**), supporting the diagnosis of DCIS (IHC).


A
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STATISTICAL ANALYSIS

Patients with DCIS as the highest-stage lesion ($n = 154$) and upstaging to microinvasive or invasive carcinoma ($n = 32$) were compared for pathological and clinical features. Categorical variables were tested between groups by the use of Fisher's exact or chi-square tests. Continuous variables were tested with *t*-tests or Wilcoxon rank tests as appropriate, according to the distribution. Logistic models were used to determine associations between covariates and upstaging. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. A *P*-value of <0.05 was considered to be significant.

Results

CLINICOPATHOLOGICAL FEATURES CORRELATING WITH UPSTAGING

Of the 186 patients included in this study, 69 (37.1%) underwent mastectomy and 117 (62.9%) underwent lumpectomy for definitive surgical treatment.

Ductal carcinoma *in situ* remained the highest-stage lesion on excision in 154 of the cases (82.8%); these included 13 cases with no residual neoplasm that were smaller in size (mean 4 mm, range 0.1–8 mm) and more frequently low grade (6/13; 46.1%) and ER-positive (11/13; 84.6%).

Thirty-two patients (17.2%) were upstaged to either microinvasive (nine) or invasive (23) ductal carcinoma on excision, with a mean lesion size of 5 mm (range <1–15 mm). On univariable analysis, the presence of a radiological mass ($P = 0.0004$), periductal chronic inflammation ($P = 0.03$) and distorting periductal sclerosis ($P < 0.0001$) were significantly associated with upstaging to microinvasive or invasive ductal carcinoma on excision (Table 1). However, on multivariable analysis, only the presence of a radiological mass ($P = 0.009$) and distorting sclerosis ($P = 0.0005$) remained significantly associated with upstaging.

Comparison of the features of the excision specimens between the two groups demonstrated that multifocal DCIS was significantly associated with upstaging to invasive disease ($P < 0.0001$) (Table 2).

CASES WITH DISTORTING SCLEROSIS

All cases of DCIS with distorting sclerosis evaluated by IHC staining for myoepithelial markers had positive myoepithelial staining that was patchy in nature (Figure 1D), except for two cases that were were noted to have strong, diffuse staining (Figure 2A, B). Review of the subsequent excision specimens in these two cases confirmed DCIS involvement of sclerosing adenosis.

None of the patients with distorting sclerosis had undergone previous biopsy in the same breast quadrant, excluding sclerosis resulting from reparative change.

Distorting sclerosis was associated with high grade, comedonecrosis, extensive cancerization of lobules, extensive periductal chronic inflammation, and ER/PR negativity (Table 3). Distorting sclerosis was not associated with the other clinicopathological features examined in this study. It is of note that there was no significant difference regarding the presence of a mass lesion, which was seen in 12 of 50 (24%) of cases with and 25 of 136 (18.4%) cases without distorting sclerosis.

Mass lesion was more frequently seen in cases with distorting sclerosis with upstaging on excision (8/21; 38.1%) than in those without (4/29; 13.8%). Of the 21 patients with distorting sclerosis that had upstaging, the majority underwent stereotactic core biopsy (19/21; 90.5%), the rate being similar to the overall rate (Table 1).

SLNBS

Sentinel lymph node biopsy was performed in 84 of 186 patients (45.2%), and was more frequently performed in patients who had undergone mastectomy (56/69; 81.2%) than in those who had undergone breast-conserving therapy (28/117; 23.9%) ($P < 0.0001$).

Of the patients who underwent SLNB, 83 of 84 (98.8%) had negative sentinel lymph nodes, and one of 84 (1.2%) had a micrometastasis. The single patient with a micrometastasis was a 43-year-old woman with a 150-mm span of suspicious microcalcifications and associated density on mammography. Core biopsy showed high-grade DCIS with comedonecrosis and microcalcifications that was ER-positive (97%) and PR-positive (15%). Distorting sclerosis was also present. Simple mastectomy revealed a 15-mm focus of invasive ductal carcinoma and extensive DCIS. The patient had micrometastatic carcinoma in one of eight sentinel lymph nodes, and later surgery for axillary lymph node dissection revealed 22 additional lymph nodes that were negative for carcinoma.

Reoperation was performed for SLNB in 22 of 84 patients (26.2%): 11 with pure DCIS, and 11 with upstaging on excision. Eight of the 11 (72.7%) patients with upstaging had distorting sclerosis on core biopsy.

Table 1. Preoperative clinicopathological features in patients with ductal carcinoma *in situ* (DCIS) as the final pathological lesion and in patients upstaged to microinvasive or invasive carcinoma on final excision

	Final pathological diagnosis		
	DCIS (n = 154)	Microinvasive or invasive carcinoma (n = 32)	P-value
Patient age (years), mean (range)	57.7 (32.0–87.9)	55.9 (43.1–79.2)	0.42
Radiological mass, no. (%)	23 (14.9)	14 (43.8)	0.0004
Radiologic calcifications (%)	140 (90.9)	31 (96.9)	0.47
Biopsy procedure, no. (%)			
Stereotactic	138 (89.6)	29 (90.6)	0.30
8-gauge	70 (45.2)	19 (59.4)	
11-gauge	68 (44.2)	10 (31.2)	
Ultrasound-guided (14 gauge)	15 (9.7)	2 (6.3)	
MRI-guided	1 (0.7)	0 (0)	
Office (clinician-performed)	0 (0)	1 (3.1)	
Median number of sites biopsied (range)	1 (1–3)	1 (1–2)	0.11
Median number of cores submitted per site (range)	6 (1–19)	6 (4–12)	0.29
Mean linear extent of core involvement (mm) (range)	6 (1–17)	7 (2–17)	0.08
Nuclear grade, no. (%)			
Low	20 (13)	1 (3.1)	0.16
Intermediate	52 (33.8)	9 (28.1)	
High	82 (53.2)	22 (28.8)	
Comedonecrosis, no. (%)			
None	55 (35.7)	8 (25)	0.36
Focal	50 (32.5)	10 (31.3)	
Extensive	41 (26.6)	14 (43.7)	
Primary architectural pattern, no. (%)			
Solid	70 (45.5)	13 (40.6)	0.65
Cribriform	27 (17.5)	4 (12.5)	
Comedo	36 (23.4)	11 (34.4)	
Micropapillary	6 (3.9)	0 (0)	
Papillary	12 (7.8)	3 (9.4)	
Other	3 (1.9)	1 (3.1)	

Table 1. *(Continued)*

	Final pathological diagnosis		
	DCIS (n = 154)	Microinvasive or invasive carcinoma (n = 32)	P-value
Cancerization of lobules, no. (%)			
None	68 (44.2)	10 (31.3)	0.24
Focal	45 (29.2)	9 (28.1)	
Extensive	41 (26.6)	13 (40.6)	
Periductal inflammation, no. (%)			
None	56 (36.4)	10 (31.2)	0.03
Focal	56 (36.4)	6 (18.8)	
Extensive	42 (27.2)	16 (50)	
Oestrogen receptor expression, no. (%)			
Negative (<1%)	32 (20.8)	6 (18.7)	0.10
Weak (1–10%)	3 (2)	3 (9.4)	
Positive (>10%)	119 (77.3)	23 (71.9)	
Progesterone receptor expression, no. (%)			
Negative (<1%)	45 (29.2)	12 (37.5)	0.24
Weak (1–10%)	11 (7.1)	0 (0)	
Positive (>10%)	98 (63.6)	20 (62.5)	
Periductal fibrosis, no. (%)			
None	19 (12.3)	2 (6.3)	0.25
Focal	58 (37.7)	9 (28.1)	
Extensive	77 (50)	13 (40.6)	
Distorting sclerosis, no. (%)			
None	125 (81.2)	11 (34.4)	<0.0001
Focal	24 (15.6)	17 (53.1)	
Severe	5 (3.2)	4 (12.5)	

MRI, Magnetic resonance imaging.

Discussion

The present study evaluated a combination of clinical and pathological features in patients diagnosed with DCIS on core biopsy. Although pure DCIS theoretically has no metastatic potential, patients are not infrequently upstaged to microinvasive or invasive carcinoma, owing to incomplete sampling of lesions on core biopsy. Because invasive disease necessitates axillary staging, many patients must undergo a second operation unless staging was performed at the time of excision. Axillary staging at the time of excision for all cases of DCIS is not a viable alternative, owing to the low risk of axillary lymph node involvement and potential adverse effects associated with the procedure. Thus, clinicopathological features allowing clinicians to determine which patients are at risk for upstaging on excision would be immensely helpful to

Table 2. Postoperative clinicopathological features in patients with ductal carcinoma *in situ* (DCIS) as the final pathological lesion and in patients upstaged to microinvasive or invasive carcinoma on final excision

	Final pathological diagnosis		
	DCIS (n = 154)	Microinvasive or invasive carcinoma (n = 32)	P-value
Multifocal disease, no. (%)			
None	95 (61.7)	5 (15.6)	<0.0001
DCIS	59 (38.3)	23 (71.9)	
Invasive ± DCIS	0 (0)	4 (12.5)	
Calcifications in DCIS, no. (%)	142 (92.2)	31 (96.9)	0.70
Final surgery, no. (%)			
Lumpectomy	101 (65.6)	16 (50)	0.10
Mastectomy	53 (34.4)	16 (50)	

minimize the unnecessary use and maximize the utility of SLNB in appropriate patients.

In our study, the rate of upstaging to microinvasive or invasive carcinoma was 17.2%, which is consistent with the range of 8–47% reported in the literature, and comparable with the 25.9% reported in a meta-analysis of 7350 patients diagnosed with DCIS.[2–18,21] Multivariable analysis of clinicopathological features demonstrated that the preoperative features of radiological mass (P = 0.009) and distorting sclerosis on biopsy (P = 0.0005) were significantly associated with upstaging to microinvasive or invasive carcinoma.

Similar to our findings, several studies have found an association between the presence of a mass on imaging and/or clinical examination and upstaging on excision.[2,3,5–7,9,10,12,13,16–18] When lesions were stratified by size, a meta-analysis found that lesions >20 mm were strongly associated with underestimation of invasive carcinoma on biopsy.[21]

To our knowledge, this is the first study to evaluate the significance of distorting sclerosis and upstaging of DCIS to invasive carcinoma on definitive excision. We defined distorting sclerosis as desmoplasia or dense fibrosis in surrounding stroma causing irregular angulation of glands involved by DCIS. This is in contrast to periductal fibrosis, which we considered to be encasement of ducts by concentric non-distorting fibrosis. All cases with distorting sclerosis lacked

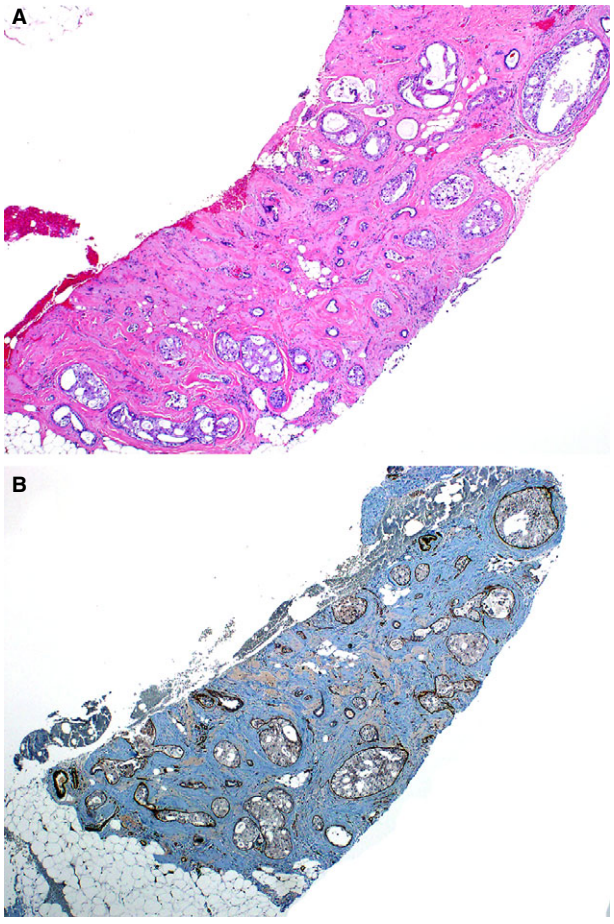

Figure 2. **A**, High-grade apocrine ductal carcinoma *in situ* involving sclerosing adenosis (haematoxylin and eosin). **B**, Corresponding strong, positive muscle-specific actin immunohistochemical staining highlighting myoepithelium throughout.

obvious invasion according to morphology; however, the cases with severe distorting sclerosis showed such distortion that immunohistochemical staining for myoepithelial markers was performed to verify the *in-situ* nature. Chivukula *et al.*[22] examined 35 cases of high-grade DCIS with thick periductal scarring and variable lymphoid infiltrates. They coined the phenomenon 'regressive changes', akin to the changes seen in regressive changes of malignant melanoma. They outlined several stages of regression: a dense periductal lymphocytic infiltrate, followed by increasing periductal fibrosis, and eventual obliteration of neoplastic cells and the duct lumen with attenuation of the inflammatory response. In their study of high-grade DCIS with and without regressive changes, they noted a higher propensity for upstaging to invasive carcinoma on excision in the group with regressive changes (20% versus 4%). Although cases of distorting sclerosis showed intact myoepithelial

Table 3. Histological features associated with ductal carcinoma *in situ* with distorting sclerosis

	No distorting sclerosis (n = 136)	Distorting sclerosis (n = 50)	P-value
Nuclear grade, no. (%)			
Low	21 (15.5)	0 (0)	<0.0001
Intermediate	55 (40.4)	6 (12)	
High	60 (44.1)	44 (88)	
Comedonecrosis, no. (%)			
None	57 (41.9)	6 (12)	<0.0001
Focal	47 (34.6)	13 (26)	
Extensive	32 (23.5)	31 (62)	
Cancerization of lobules, no. (%)			
None	69 (50.7)	9 (18)	0.0001
Focal	37 (27.2)	17 (34)	
Extensive	30 (22.1)	24 (48)	
Periductal inflammation, no. (%)			
None	61 (44.9)	5 (10)	<0.0001
Focal	48 (35.3)	14 (28)	
Extensive	27 (19.8)	31 (62)	
Oestrogen receptor expression, no. (%)			
Negative (<1%)	20 (14.7)	18 (36)	0.0002
Weak (1–10%)	2 (1.5)	4 (8)	
Positive (>10%)	114 (83.8)	28 (56)	
Progesterone receptor expression, no. (%)			
Negative (<1%)	30 (22.1)	26 (52)	0.0004
Weak (1–10%)	9 (6.6)	2 (4)	
Positive (>10%)	97 (71.3)	22 (44)	

staining, the staining was patchy in most cases, like that described by Chivukula *et al.*[22] This raises the possibility that distorting sclerosis and regressive changes may have a related aetiology. Chivukula *et al.* proposed that the increased rate of invasive carcinoma may be attributable to a decrease in the density of the myoepithelial layer, allowing neoplastic cells to easily cross the unprotected basement membrane. Like the cases with regressive change, cases with distorting sclerosis were more frequently high grade and had prominent periductal chronic inflammation.[22]

Sclerosing lesions, such as sclerosing adenosis and radial scars, are associated with a 1.5-fold to two-fold increase in the risk of developing invasive breast carcinoma, which is similar to the level of risk associated with other proliferative lesions without atypia.[23–25] Yoshida *et al.*[26] showed that patients with sclerosing adenosis involved by DCIS had a significantly higher rate of synchronous or metachronous bilateral invasive breast carcinoma than patients with DCIS in the absence of sclerosing adenosis. These findings raise the possibility that an underlying sclerosing lesion may accelerate the progression from DCIS to invasive carcinoma. In our study, severe distorting sclerosis on core biopsy represented DCIS involving sclerosing adenosis in two cases. These cases showed strong myoepithelial immunostaining, which aided significantly in ruling out invasive carcinoma and was easily distinguished from the pattern of reduced, patchy myoepithelial staining in distorting sclerosis. The paucity of involvement by sclerosing lesions in our cohort suggests that the association between distorting sclerosis and invasive carcinoma is probably not attributable to risk caused by a background sclerosing lesion, but is actually a real, independent risk factor for invasive disease.

Severity of periductal chronic inflammation was a significant predictor of upstaging to invasive carcinoma on univariable analysis (P = 0.03) but not on multivariable analysis. This association was most influenced by a skew towards more extensive chronic inflammation in patients with upstaging on excision. The interface between the immune system and cancer and how their interaction affects disease progression has become an important area of research interest. CD4+/CD25+ regulatory T cells (TRs), which typically suppress T-cell proliferation and cytokine production, are found in increased numbers in autoimmune disease and numerous cancers, including breast cancer, and are considered to be markers of poor clinical outcome. Both Bates *et al.* and Lal *et al.*[27,28] showed that TR numbers progressively increase from benign breast tissue to DCIS to invasive carcinoma, and serve as a marker of breast cancer progression. Our findings of the association between extensive periductal inflammation on core biopsy and subsequent upstaging on excision supports the current hypothesis that an increased number of TRs results in suppression of normal host immune defences, facilitating tumour progression.

In our cohort, SLNB was performed at the time of excision in 18 of 32 (56.3%) patients upstaged to microinvasive or invasive carcinoma according to

final pathology findings, whereas reoperation was performed in 11 of the 14 remaining patients for whom SLNB was recommended. Among patients with pure DCIS as a final diagnosis, 55 of 154 (35.7%) had unnecessary SLNBs. If every patient in our study cohort who either presented with a radiological mass or showed DCIS with distorting sclerosis on core biopsy had undergone SLNB at the time of excision, 27 of the 32 (84.3%) with the final diagnosis of microinvasive or invasive carcinoma would have undergone concurrent SLNB. As compared with the current clinical practice at our institution, 11 additional patients with a final diagnosis of microinvasive or invasive carcinoma would have undergone SLNB at excision instead of requiring reoperation, and seven patients with pure DCIS would have been spared an unnecessary procedure.

Distorting sclerosis is a novel feature in DCIS that appears to be predictive of upstaging to microinvasive or invasive cancer on excision. Distorting sclerosis may be related to 'regressive change', and shows a similar intact but reduced myoepithelial density, which was previously theorized to allow for greater ease of invasion into the stroma. IHC staining for myoepithelial markers may be helpful in differentiating DCIS with distorting sclerosis from true microinvasion and from DCIS involving sclerosing lesions. However, identification of DCIS with distorting sclerosis via routine histological examination may often be sufficient. When it is present, a statement may be included in the pathology report to alert the surgeon that higher-stage disease may be present and that SLNB should be considered at the time of excision.

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Conflict of interests

The authors declare that there are no conflicts of interest.

Author contributions

L. L. Walters performed the research and wrote the manuscript. J. Pang performed the research and edited the manuscript. L. Zhao analysed the data. J. M. Jorns designed the research study, performed the research, analysed the data, and edited the manuscript.

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