Assessing Invasion Criteria in Fine Needle Aspirates from Breast Carcinoma Diagnosed as DCIS or Invasive Carcinoma

Can We Identify an Invasive Component in Addition to DCIS?

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Objective

To evaluate invasion criteria in fine needle aspiration cytology (FNAC) of histologically diagnosed breast ductal carcinoma in situ (DCIS) and invasive carcinoma and to evaluate their usefulness in identifying an invasive component in addition to DCIS.

Study Design

The material consisted of 331 smears diagnosed as suspicious for or consistent with DCIS and in which histology had shown either DCIS or invasive ductal carcinoma. All smears were reevaluated for the following invasion criteria: invasion of fat or fibrous tissue fragments, fibroblast proliferation, cell-poor elastoid tissue fragments, tubular structures and intracytoplasmic vacuoles.

Results

All invasion criteria except cytoplasmic vacuoles correlated with invasiveness, but none of them were found exclusively in invasive lesions. Pseudoinvasion in fibrous or fatty tissue fragments were found in 8 cases of histologic pure DCIS. One DCIS (0.4%) revealed ≥ 2 invasion features as well as 22 invasive carcinomas (20.7%), representing 7.4% of all cases.

Conclusion

Using established invasion criteria, practically no pure DCIS lesion will be diagnosed as invasive on FNAC, but one will identify only a subset of cases harboring an invasive component. (Acta Cytol 2006;50:263–270)

Keywords: breast cancer; aspiration biopsy, fine-needle; ductal carcinoma in situ.

Invasion criteria will identify only a subset of DCIS cases harboring an additional invasive component.

The cytologic diagnosis of ductal carcinoma in situ (DCIS) in breast fine needle aspiration cytology (FNAC) and the distinction between DCIS and invasive carcinoma has been, and still is, the subject of much discussion and controversy in the cytologic community and literature.[1-4] The cytologic criteria of high grade (G) DCIS are well described, and the specificity is high.[5-11] The diagnostic triad consists of highly atypical carcinoma cells in groups, 3-dimensional cell aggregates and single cells, comedo-type necrosis and amorphous microcalcifications.[7]

Experience with non–high G DCIS is more limited,[7,12] but in a recent study we described the morphologic characteristics of 51 cases of non–high G DCIS

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Presented in part at the 15th International Congress of the International Academy of Cytology, Santiago, Chile, April 11–15, 2004.

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Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

Received for publication January 20, 2005.

Accepted for publication May 20, 2005.

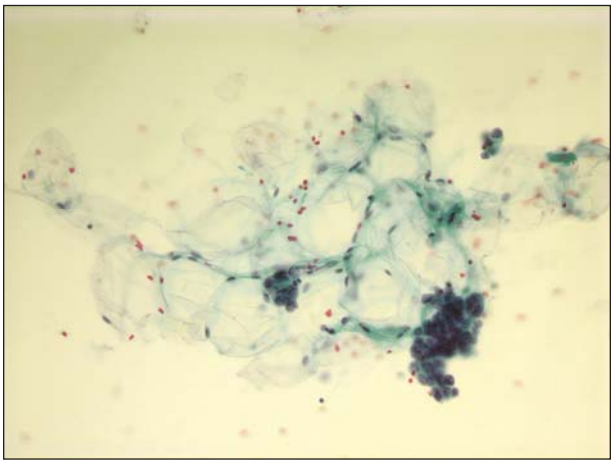

Figure 1 Fatty tissue with infiltration of carcinoma cells from an invasive ductal carcinoma (Papanicolaou stain, ×20).

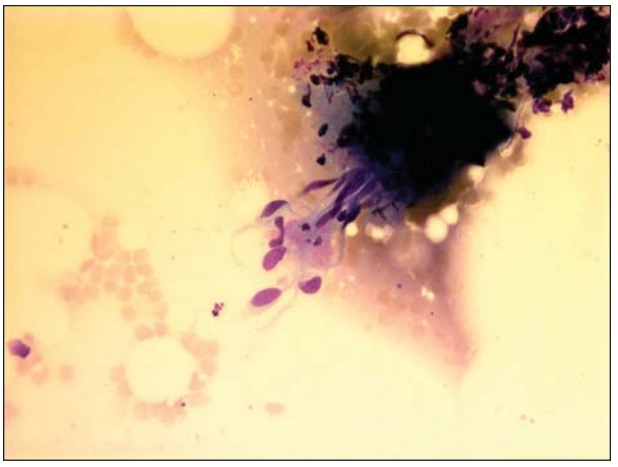

Figure 3 Proliferating fibroblasts in smear from an invasive carcinoma (Giemsa stain, ×40).

in breast FNAC.[13] The morphologic features include discrete to moderate nuclear atypia; 3-dimensional, cribriform and solid epithelial cell aggregates; and micropapillary groups and monolayered sheets. A variable number of dissociated, single-lying carcinoma cells are often present.

Some studies have described and evaluated invasion criteria[1,14-16]; that allows definite identification of an invasive lesion. These criteria include invasion in fat or fibrous tissue fragments, fibroblast proliferation, cell-poor elastoid tissue fragments, tubular structures and intracytoplasmic vacuoles. Using these criteria, some, but not all, invasive carcinomas can be identified on FNAC smears.

Many cytopathologists remain reluctant to give a specific diagnosis of both DCIS and invasive vs. in situ carcinoma. As a consequence, many radiologists and surgeons prefer core needle biopsies, especially in the workup of mammographically detected microcalcifications.

The aim of this study was to evaluate the above invasion criteria in FNAC of histologically diagnosed breast DCIS and invasive carcinoma and to evaluate their usefulness in identifying an invasive component in addition to DCIS.

Materials and Methods

The material consisted of 331 breast FNAC that had been diagnosed as suspicious for or consistent with ductal (including papillary) carcinoma in situ, high G

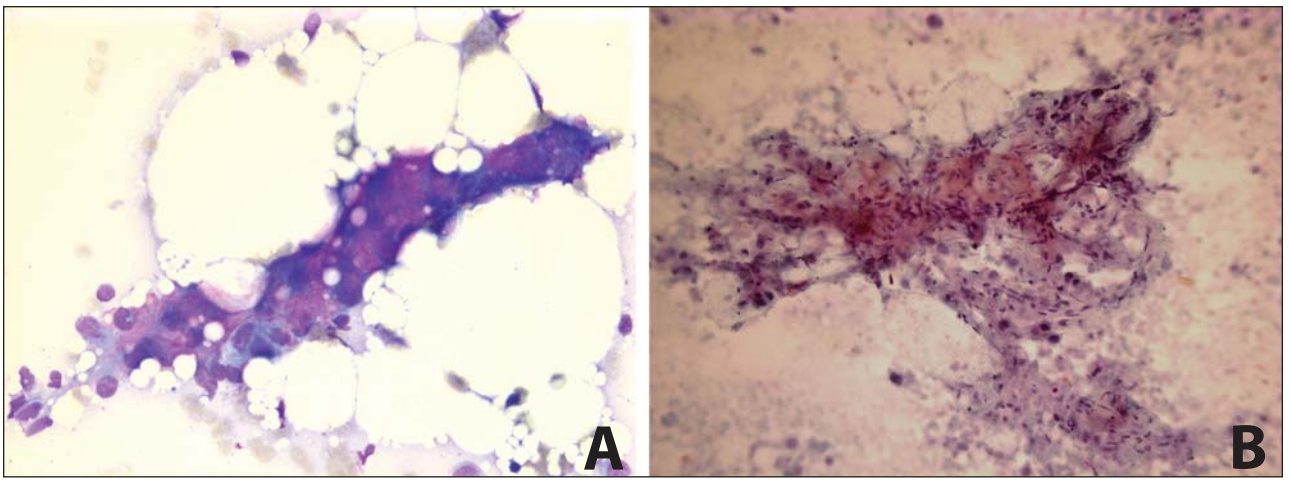

Figure 2 (A) Stromal/fibrous tissue fragment with invading carcinoma cells from an invasive carcinoma. (B) Carcinoma cells infiltrating a stromal tissue fragment from an invasive ductal carcinoma (A, Giemsa stain, ×40; B, Papanicolaou stain, ×20).

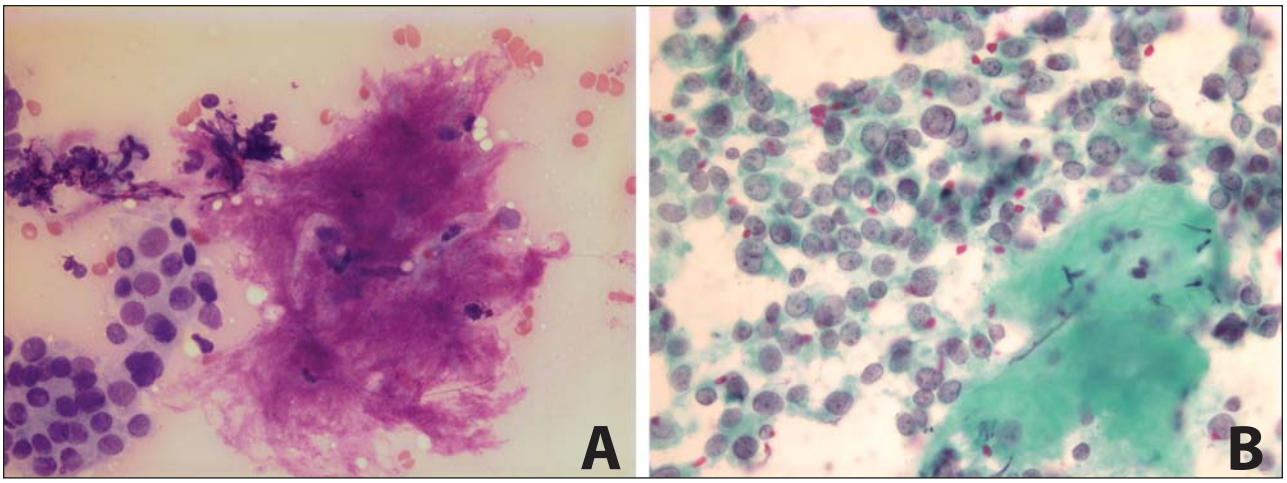

Figure 4 Cell-poor elastoid stromal fragments. (A) Smear from an invasive carcinoma. (B) Smear from G3 DCIS with microinvasion (A, Giemsa stain, ×40; B, Papanicolaou stain, ×20).

or non–high G, and in which histology had shown either DCIS or invasive ductal carcinoma. In addition, there were cases diagnosed as "carcinoma cells" (diagnosed before 1994) or invasive carcinoma in which histology showed pure DCIS. All cases had been diagnosed during 1990–2003. In a recent paper we extensively evaluated and described the pure DCIS cases from this material.[13] The extent of overdiagnosis of histologic DCIS as invasive on FNAC has been elucidated in a previous paper.[17] Both palpable and nonpalpable lesions were included.

All smears were evaluated by 1 observer for the following invasion criteria: invasion of fat or fibrous tissue fragments, fibroblast proliferation, cell-poor elastoid tissue fragments, tubular structures and intracytoplasmic vacuoles (Figures 1–6). Two or more of the features were considered suggestive of invasion, according to the criteria of Bondeson et al.[15]

The histologic grading was reevaluated in all cases.[18,19] TNM grading was retrieved from the histology files of the department and from pathology records obtained from external pathology departments. Histologic G (G) was used in all tables, figures and text. Radiologically, the vast majority were mammographically detected microcalcifications without any sign of tumor/density/asymmetry and had been aspirated using stereotaxic guidance. A few had appeared as a tumor on mammography or ultrasonography (US). The radiologic images were not reevaluated. Statistical analysis (χ^2, p values) was done using SPSS® 12.0 (Chicago, Illinois, U.S.A.) for Windows® (Microsoft Corp, Redmond, Washington, U.S.A.). Sentinel node dissection has been done at our hospital since 2000. Given a preoperative cytologic diagnosis of invasive carcinoma and, since 2001, also DCIS G3, the surgeon performs sentinel node dissection when primary surgery on the breast is performed.

The material was retrieved and evaluated with the permission of the head of the Department of Pathology.

Results

The details of grading, TNM and invasion criteria are shown in Tables I–VI. Pure DCIS was found in 225 cases. All invasion criteria except cytoplasmic vacuoles correlated with invasiveness (Table II). One or more invasion features were found in 15 of 53 G1/G2 DCIS and 55 of 172 G3 DCIS (21%) (Table III). Two or more invasion criteria were found in 5 (2.9 %) of the G3 DCIS (Table IV) but in none of the G1/G2 cases. Pseudoinvasion in fibrous and fatty tissue fragments

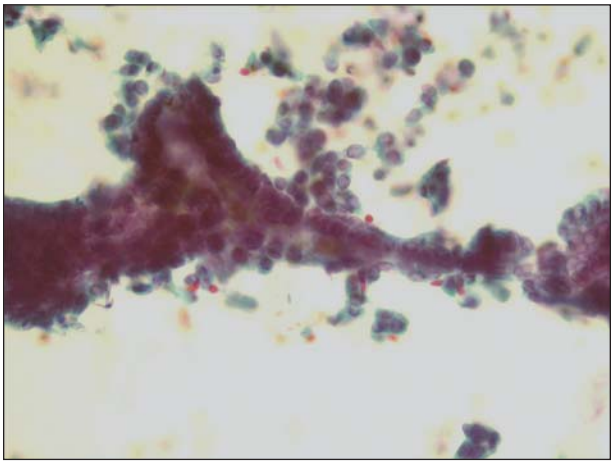

Figure 5 Tubular structure in smear from an invasive ductal carcinoma (Papanicolaou stain, ×40).

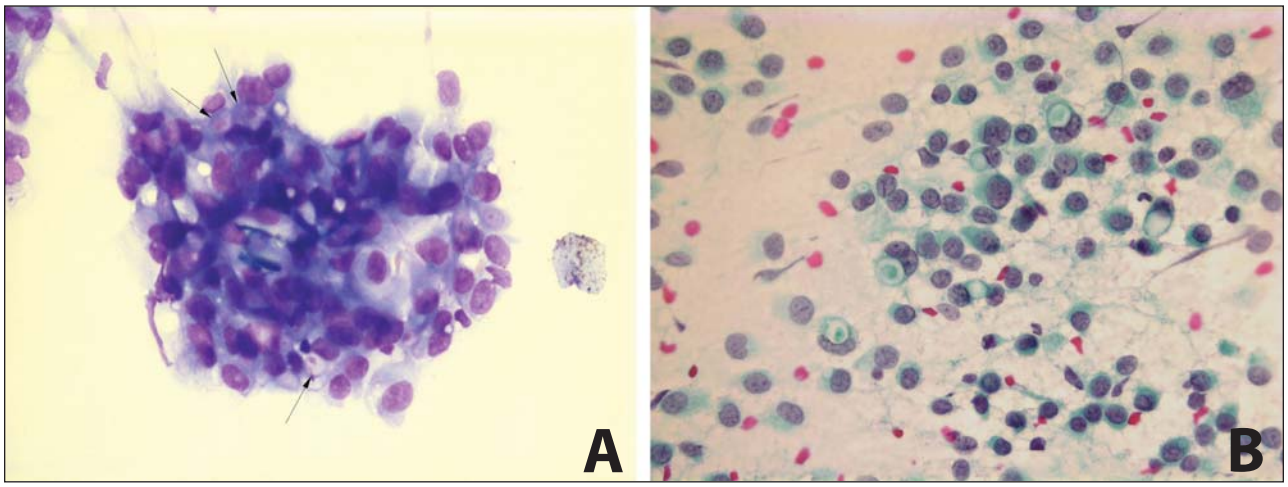

Figure 6 Cytoplasmic vacuoles (arrows). (A) Smear from G3 DCIS. (B) Smear from invasive carcinoma (A, Giemsa stain, ×40; B, Papanicolaou stain, ×40).

was found in 2 and 6 cases of histologic pure DCIS, respectively. Follow-up (>3 years) has not revealed metastasis or local/regional recurrences in any of these cases. True tubular structures were demonstrated in 1 case of pure DCIS. On histology this case showed cancerization in preexisting sclerosing adenosis.

Invasive carcinoma was demonstrated in 106 cases (31.7%). Of these, 23 (21.7%) were G1/G2, and 83 (78.3%) were G3. The accompanying DCIS component was G1 in 18 cases (17%), whereas the rest were G3. There was no difference in the percentage of DCIS G1 and G3 with a histologic invasive lesion (25% and 22%, respectively) (Table III). One or more invasion feature was demonstrated in 67 cases (63.2%). Two or more invasion criteria were found in 26 (24.5%) of the invasive cases—i.e., in 4 of the G1/G2 tumors and 22 of the G3 tumors (Tables V and VI).

Totally, ≥2 invasion criteria were demonstrated in 31 of 331 (9.4%) cases. If "cytoplasmic vacuoles" is omitted from the invasion criteria, only 1 G3 DCIS (0.4%) would reveal ≥2 invasion features, as would 22 of the invasive carcinomas (20.7%), representing 7.4 % of all cases.

Smears from 2 pT3 tumors were devoid of invasion features. One tumor measured 8 cm, and histology showed a mixture of invasive carcinoma and G3 DCIS. The other tumor measured 5 cm, but the extent of DCIS is unknown (not reported in the external pathology report).

Axillary node positivity was found in 7% (3 of 43) pT1a, 16.6% (4 of 24) pT1b, 21.7% (5 of 23) pT1c and 37.5% (6 of 16) pT2 carcinomas. Sentinel node dissection had been done in 66 cases of pure DCIS. None were metastatic. One that was histologically diagnosed as G2 DCIS had been diagnosed as G3 on cytology. The lesion was heterogeneous, but only a small proportion of the DCIS cells had nuclear size di-

Table I *G and TNM of Histologic Specimens*

	G			
TNM	**1**	**2**	**3**	**Summary**
pT				
is (Extension 1–90 mm with a mean of 21.7 mm)	35	18	172	225 = 67%
1a (DCIS extension 6–60 mm in diameter with a mean of 24.6 mm)	3	4	34	41 = 12%
1b (DCIS extension 7–70 mm in diameter with a mean of 22 mm)	6	2	16	24 = 7.2%
1c (DCIS extension 3–60 mm in diameter with a mean of 21.5 mm)	3	2	18	23 = 7%
2 (DCIS extension 20–50 mm with a mean of 35.5 mm)	3		13	16 = 4%
3 (see Results)			2	2
Summary	50	26	256	331

DCIS extension is in addition to the invasive component.

Table II *Invasion Criteria Compared to DCIS vs. Invasive Carcinoma*

Invasion criteria	pTis	Invasive lesions	χ^2, p value
Cytoplasmic vacuoles	36 (16.7 %)	15 (14.3 %)	NS
Proliferation of fibroblasts	7 (3.3 %)	20 (18.9 %)	< 0.001
Elastoid stromal fragments	27 (12.6 %)	27 (25.5.%)	< 0.014
Tubular structures	1 (0.5 %)	7 (6.6 %)	0.003
Infiltration in fragments of fat	6 (2.8 %)	15 (14.2 %)	< 0.001
Infiltration in fibrous tissue fragments	2 (0.9 %)	13 (12.3 %)	< 0.001

agnostic of G3 DCIS on histology, and it was thus classified as G2. Sentinel node dissection had also been done in 1 case that histologically was G1 DCIS. Cytologically this was a G3 lesion, also on review, but no high G component could be identified on histology.

Discussion

In our experience, the cytologic criteria for DCIS, both high G and non–high G, are characteristic and can be identified with confidence.[13] An additional invasive component, however, might not be easy to identify. In a context of mammographically suspicious microcalcifications and an FNAC diagnosis of DCIS (without any consideration as to a palpable or nonpalpable lesion), we found invasive carcinoma (with an additional DCIS component) in approximately 30% of cases. In this setting the invasive component would not have been visualized on the mammogram or US and thus not targeted on FNAC. In our experience, the invasive component is not always found within the DCIS lesion. It can be found anywhere in the breast but is usually in the vicinity of the in situ component. In the present study, 70.7% of invasive carcinomas were ≤ 10 mm, representing pT1a and pT1b (Table I), and were small tumors that most probably had not been identified on mammography and/or US. This had no effect on the primary surgery, as it depends on the extension of the radiologic lesion and not whether it is invasive or pure DCIS.[20] Since the advent of the sentinel lymph node technique in breast cancer surgery, the distinction between invasive and high nuclear G DCIS is not necessarily critical, as it might be justified to remove the sentinel node or nodes in both groups.[20]

A radiologic tumor or density will almost always represent an invasive carcinoma.[21,22] If identified radiologically, it will be sampled directly. A DCIS component within an invasive carcinoma might reveal the typical features of cytologic DCIS on the aspirated smears. This might be the cause of some confusion and uncertainty, resulting in a defensive diagnosis, especially when definite invasion criteria are lacking. Our findings in this series concur with those of Bondeson et al[15]: only a subset of invasive carcinomas demonstrated definite (≥ 2) invasion criteria. In the clinical/radiologic setting of probable DCIS, only 7.4% of cases will demonstrate definite invasion criteria on FNAC smears—i.e., in 1 of 5 of the invasive carcinomas and at the cost of 1 false positive. Thus, the usefulness of invasion criteria in this setting is limited.

In nonpalpable lesions with a cytologic diagnosis of

Table III *Invasion Criteria Compared to TNM and G*

pTG	Invasion criteria	No Invasion criteria	1 Invasion criterion	≥ 2 Invasion criteria	Subtotal
pTis G1		27	8		35
pTis G2		11	7		18
pTis G3		117	50	5 (2.9 %)	172
pT1aG3 isG3		16	15	3 (8.8%)	34
pT1bG3 isG3		5	2	9 (56%)	16
pT1cG3 isG3		3	7	8 (44%)	18
pT2G3 isG3		4	7	2 (15.4%)	13
pT3 G3		2			2
pT1aG1 isG1		2	1		3
pT1bG1 isG1		3	1	1	5
pT1cG1 isG1		1	2	3	
pT2G1 isG1		1	2		3
pT1aG2 isG1		2	2		4
pT1bG2 isG3			1	1	2
pT1cG2 isG3			2		2
pT1bG1 isG3					1
Subtotal				31	331

Table IV *Details of Pure G3 DCIS Cases with > 2 Invasion Criteria*

Invasion criteria	Case 1, 35 mm in diameter	Case 2, 8 mm in diameter	Case 3, 15 mm in diameter	Case 4, 15 mm in diameter	Case 5, 20 mm in diameter
Invasion in fatty tissue	X				
Invasion in fibrous tissue		X			
Proliferation of fibroblasts					
Cell-poor elastoid tissue fragments		X	X	X	X
Tubular structures		X			
Cytoplasmic vacuoles	X	X	X	X	X

DCIS, the histologic diagnosis is invasive carcinoma in 18.7% of cases.[23] This is the same figure that is usually given for core biopsies,[24-27] in which targeting the invasive component also is the main problem. In contrast, practically all palpable lesions will be invasive.[28] Cytoplasmic vacuoles are a characteristic finding in many invasive lobular carcinomas. They are equally common in lobular carcinoma in situ and atypical lobular hyperplasia. In addition, cytoplasmic vacuoles may be found in invasive ductal carcinoma and DCIS. They are a marker of a neoplastic or preneoplastic breast lesion. In the present study, cytoplasmic vacuoles were found in approximately the same percentage of cases in both DCIS and DCIS with an invasive component. This feature was not a useful marker of invasiveness in the present context and should not be used.

Infiltration of single or small groups of carcinoma cells in fragments of fat and/or fibrous tissue has been evaluated as a strong predictor of an underlying invasive lesion.[1,16] However, they should not be relied upon as single features. We found seeming invasion in fat (6) or fibrous (2) tissue fragments in 8 cases of histologically pure DCIS. There is always the possibility that the invasive lesion has not been sampled for histology. The paraffin blocks of the above cases have not been serially sectioned, but an adequate number of sections have been investigated. Also, there is no evidence of metastasis or local/regional recurrence in any of the cases after > 3 years of follow-up. We have applied very strict criteria for both features in order to avoid false or pseudoinvasive carcinoma cells. Apparent infiltration in stromal tissue (fat or fibrous) fragments is a rare finding and, in our material, not 100% specific to an invasive lesion. Any 1 of these 2 features should not be considered adequate for diagnosis of an invasive lesion but only when ≥ 1 of the other invasion criteria are also present.

Cell-poor elastoid stromal fragments (12.6%) as well as fibroblasts (3.3%) may be found in histologically pure DCIS and probably represent periductal fibrosis and elastoid degenerative changes. Fragments of elastoid stroma were found in 25% of the invasive lesions as well as in 10% of pure DCIS, and this feature should also be evaluated cautiously.

Tubular structures have very high specificity for invasiveness.[1,15] Theoretically, true tubules are not a feature of DCIS and should not be found at all. However, pitfalls and look-alikes exist, as demonstrated in 1 of our cases (Table IV, case 2). Tubular structures are not unique to carcinomas but may also be encountered in adenosis of the breast.[29] Coexisting DCIS with cancerization of adenosis (as in our case) may lead to true tubular structures composed of atypical epithelial cells.

Table V *Details of pT1a-pT2 (G3) Cases with > 2 Invasion Criteria (22 Cases)*

pT	Invasion criteria
pT1a	Proliferation of fibroblasts + cytoplasmic vacuoles (1 case)
	Proliferation of fibroblasts + elastoid tissue fragments + cytoplasmic vacuoles (2 cases)
pT1b	Elastoid tissue fragments + cytoplasmic vacuoles (2 cases)
	Proliferation of fibroblasts + tubular structures (2 cases)
	Invasion in fatty tissue + elastoid tissue fragments (1 case)
	Invasion in fibrous tissue fragments + cytoplasmic vacuoles (1 case)
	Invasion in fatty tissue + invasion in connective tissue + elastoid tissue fragments (1 case)
	Invasion in fatty tissue + invasion in fibrous tissue + elastoid tissue fragments + tubular structures (1 case)
	Invasion in fibrous tissue + elastoid tissue fragments + tubular structures + cytoplasmic vacuoles (1 case)
pT1c	Proliferation of fibroblasts + elastoid tissue fragments (2 cases)
	Proliferation of fibroblasts + cytoplasmic vacuoles (2 cases)
	Invasion in fibrous tissue + elastoid tissue fragments (1 case)
	Invasion in fatty tissue + proliferation of fibroblasts + cytoplasmic vacuoles (2 cases)
	Proliferation of fibroblasts + elastoid tissue fragments + cytoplasmic vacuoles (1 case)
pT2	Invasion in fibrous tissue + elastoid tissue fragments (2 cases)

Table VI *Details of G1/G2 Invasive Carcinomas with > 2 Invasion Criteria (4 Cases)*

pT	Invasion criteria
pT1b G1	Proliferation of fibroblasts + elastoid tissue fragments + tubular structures (1 case)
pT1c G1	Elastoid tissue fragments + cytoplasmic vacuoles (1 case) Proliferation of fibroblasts + elastoid tissue fragments (1 case)
pT1b G2	Invasion in fibrous tissue + elastoid tissue fragments + tubular structures+ cytoplasmic vacuoles (1 case)

A number of pure DCIS and invasive lesions will reveal 1 of the features associated with invasiveness (21.0% and 63.2%, respectively) on FNAC smears. If we stick to the standard set by Bondeson et al,[15] that at least 2 criteria should be demonstrated in the smear in order to diagnose the lesion as invasive carcinoma, the vast majority of in situ lesions will be correctly diagnosed as DCIS. When we omit cytoplasmic vacuoles as an invasion feature, only 1 of 225 (0.4%) DCIS cases would falsely be diagnosed as invasive.

The reproducibility of the criteria was not an issue in this study. None of the previous studies on invasion criteria have addressed the topic. Bondeson et al[15] and Klijanienko et al[16] did not comment on this at all. In studies by McKee et al[1] and Bonzanini et al,[21] 2 people had evaluated the criteria, but no interobserver variation was given. The reproducibility of the invasion criteria is unresolved.

In conclusion, invasion criteria will identify only a subset of DCIS cases harboring an additional invasive component. Thus, they are of limited value in a clinical cytologic diagnostic practice. In most of these cases of radiologic DCIS, the invasive component is small (70% <10 mm, corresponding to pT1a and pT1b), not visualized on radiology and thus not targeted by FNAC. In larger lesions (pT1c or greater), approximately 50% will reveal 2 or more invasion criteria. None of the invasion features are specific to or pathognomonic of invasiveness, but when 2 or more are found in 1 specimen, invasion might be suggested. In this study, cytoplasmic vacuoles did not correlate with invasiveness and should be omitted as an invasion feature.

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