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REVIEW

Microinvasive Carcinoma of the Breast

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Abstract The increased rate of early detection of breast cancer due to widespread mammographic screening has led to an increased incidence not only of in situ but also microinvasive carcinoma (MC). MC has been reported to have a favourable prognosis, but specific definitions have varied in the past making the clinical significance of this entity a subject of debate. In fact, although the diagnosis of MC often appears in pathology reports, this term has not been used in a consistent, standardized manner. In addition, the histological diagnosis of MC can be problematical for the pathologist due to a variety of in situ patterns and artefacts that may be misinterpreted as stromal invasion. Definitions and diagnostic criteria of MC are reviewed and discussed. Based on a review of literature, incidence of axillary lymph node involvement, according to different definitions of microinvasion, is reported.

Keywords Microinvasion · Definition · Diagnosis · Clinical significance · Breast cancer

Abbreviations

DCIS	ductal carcinoma in situ
DCIS-MI	ductal carcinoma in situ with microinvasion
IHC	immunohistochemistry
LCIS	lobular carcinoma in situ
MC	microinvasive carcinoma
NCB	needle core biopsy
VANCB	vacuum-assisted needle core biopsy
SMM-HC	smooth muscle myosin heavy chain
SLN	sentinel lymph node

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The widespread implementation of mammographic screening programmes has increased the detection of early breast cancer leading to an increased incidence of in situ as well as microinvasive carcinoma (MC).

Ductal carcinoma in situ (DCIS) is usually mammographically detected by the presence of microcalcifications and comprises 25% to 30% of breast cancer diagnosed by screening programmes. Over the past two decades, the increased use of screening mammography has resulted also in more frequent incidental diagnosis of lobular carcinoma in situ (LCIS). In addition, some cases of LCIS have been reported to be associated with calcifications: the classic form of LCIS can be associated with small calcifications identical in morphology to calcifications present in benign tissue; in contrast, large calcifications formed in central necrosis reminiscent of comedocarcinoma calcifications of DCIS have been described as mammographic pattern of pleomorphic LCIS [1–3] or lobular intraepithelial neoplasia grade 3 as proposed by Tavassoli [4].

One of the most important goals in the histological examination of in situ carcinoma is the identification of invasive focus or foci since the therapeutic decision for patients with pure in situ carcinoma differs from that of patients with in situ carcinoma associated with invasive breast cancer. A frequently encountered problem in examination of histological specimens is identifying the smallest focus or foci of invasive carcinoma, so-called microinvasion [5].

Although microinvasion is virtually almost exclusively associated with high nuclear grade-comedo ductal carcinoma in situ (DCIS), it may also be associated with other

types of DCIS and with LCIS [6] (Figs. 1 and 2). Microinvasion is reported to be related to the size/extension of associated in situ carcinoma.

The incidence rate of MC ranges from 0.68% to 2.4% [7].

Definition of Microinvasion

Lagios in 1982 [8] introduced the term "microinvasion" in breast pathology as synonymous of invasion less than 1mm. Although this term has been reported for many years, it has not been applied in a consistent, standardized manner. A variety of different definitions have been used for MC such as: DCIS with evidence of stromal invasion [9], DCIS showing focal microinvasion below the basement membrane in one or several individual ducts, but in not more than 10% of the surface of the histological sections examined [10], breast cancer cells confined to the duct system of the breast with only a microscopic focus of malignant cells invading beyond the basement membrane of the duct as determined by light microscopy [11], one or more microscopic foci of possible invasion not >1mm in greatest dimension [12–14], DCIS with limited microscopic stromal invasion below the basement membrane, but not invading more than 10% of the surface of the histological sections examined [15], the maximal extent of invasion is not more than 2mm or comprising <10% of the tumour, with 90% of DCIS [16], a single focus of invasive carcinoma ≤2mm, or up to three foci of invasion each not more than 1mm in greatest dimension [17], and a few single infiltrating tumour cells (from 1 to 15) or a few infiltrating tumour cell clusters, defined as ductal carcinoma in situ with microinvasion (DCIS-MI) type 1 and type 2 respectively [18].

This lack of an uniform definition for microinvasion has clearly contributed to the confusion regarding this entity.

The fifth edition of the AJCC Cancer Staging Manual published in 1997 [19] is the first one that recognizes a specific T substage for MC, defined as "the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1cm in greatest dimension" and formally reported it as pT1mic. The AJCC Cancer Staging Manual further stated that "when there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion and that the size of the individual foci should not be added together; the presence of multiple foci of microinvasion should however be noted and/or quantified, as it is with multiple larger invasive carcinomas" [19].

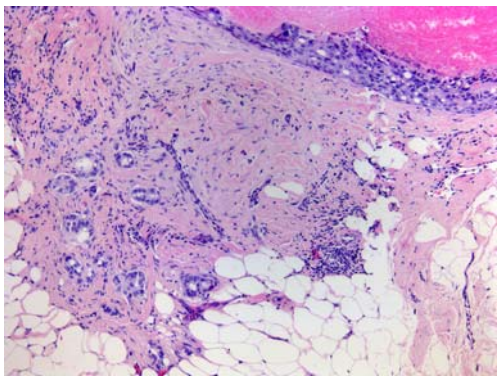

Fig. 1 Microinvasive ductal carcinoma (H&E)

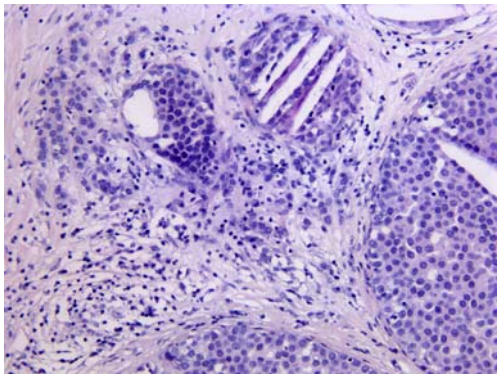

Fig. 2 Microinvasive lobular carcinoma (H&E)

Following the establishment of a National Breast Screening Programme in the UK, a Working Group of the Royal College of Pathologists produced in 1990 a document on "Pathology Reporting in Breast Cancer Screening" [13] where MC was defined as "a tumour in which the dominant lesion is non-invasive but in which there are one or more foci of infiltration, none of which measures more than 1mm (about two high power fields) in maximum diameter. Small invasive carcinomas without an in situ component are classified as invasive". In the second edition of the "Pathology Reporting in Breast Cancer Screening" published in 1995 [20] it is proposed that only when unequivocal invasion is seen outside the specialized lobular stroma, namely into the non-specialized interlobular stroma, should MC be diagnosed. If there is sufficient doubt about the presence of invasion the case should be classified as in situ carcinoma.

In the most recent edition of WHO Classification of Tumours published in 2003 [21], it is reported, in spite of the pT1mic category officially recognized by the 5th edition of the AJCC Cancer Staging Manual [19], that there is no generally accepted agreement on the definition of MC, particularly concerning the maximum diameter compatible with the diagnosis of microinvasion. On this basis MC is still considered an evolving concept that has not reached the status of a WHO-endorsed disease entity [21].

In the fourth edition of the European guidelines for quality assurance in breast cancer screening and diagnosis published in 2006 [22], formed on the major basis of UK guidelines, MC is defined as a "tumour in which the

dominant lesion is in-situ carcinoma (usually extensive high nuclear grade DCIS, rarely other types of DCIS or LCIS) but in which there are one or more, clearly separate, foci of infiltration of nonspecialized interlobular or interductal fibrous or adipose tissue, none measuring more than 1mm (about two high power fields) in maximum diameter. When there are multiple foci of MC only the size of the largest focus is used to classify the microinvasion; the presence of multiple foci of microinvasion should however be noted and/or quantified". This definition is very restrictive and tumours fulfilling the criteria are consequently rare. Not all authors accept the definition of MC that requires extension of the invasive tumour cells beyond the specialized lobular stroma because vascular channels are present both within the specialized lobular stroma and immediately around the basement membrane that invests the ducts [4, 19, 21].

A focus of invasive carcinoma 1mm or less without associated in situ carcinoma is not a MC but should be classified as invasive carcinoma and the maximum diameter measured.

Pathological Diagnosis of Microinvasion

The tumour focus/foci must invade into nonspecialized interlobular or interductal stroma. The cells deemed to be invasive must be distributed in a non-organoid pattern that does not represent tangential sectioning of a duct or a lobular structure with in-situ carcinoma. Tangentially sectioned in-situ carcinoma foci that simulate microinvasion are distributed in the specialized intralobular and periductal stroma and usually occur as compact groups of tumour cells that have a smooth border surrounded by a circumferential layer of myoepithelial cells and stroma or a thickened basement membrane [23].

At sites of microinvasive focus, tumour cells are distributed singly or as small groups that have irregular shapes reminiscent of conventional invasive carcinoma with no particular orientation [20].

The absence of basement membrane material around nests of tumour cells defines the process as being invasive. Immunohistochemistry (IHC) for basement membrane components (laminin and type IV collagen) are helpful in demonstrating the presence or absence of basement membrane [24] even though IHC for laminin and type IV collagen are reported to be often technically problematic in formalin-fixed, paraffin-embedded tissue [25]. Moreover cells of invasive cancer can still synthesize components of basement membrane around invasive nests therefore the use of basement membrane markers for the detection of stromal invasion is not recommended [26].

The presence of myoepithelial cells around nests of carcinoma cells defines the process as being in situ. IHC for myoepithelial cells has been used to help determine whether a process represents in situ carcinoma or stromal invasion [24]. A variety of markers have been used to detect myoepithelial cells; the most commonly used antibodies are: smooth-muscle myosin heavy chain (SMM-HC) and calponin; these are more specific for myoepithelial cells than actin antibodies (such as 1A4 and HHF-35 clones) and react less commonly with myofibroblasts. SMM-HC is not a perfect marker of myoepithelial cells, as it manifests slightly lower sensitivity than calponin. Therefore the optimal sensitivity and specificity of myoepithelial cell markers can be achieved when the SMM-HC marker is used in conjunction with the more sensitive but less specific marker, calponin [26].

In a recent study [27] antibodies to p63, a member of the p53 gene family, have been reported to offer excellent sensitivity and increased specificity for myoepithelial cells relative to antibodies to calponin and SMM-HC. p63 antibodies have the following diagnostic limitations: 1) they occasionally demonstrate an apparently discontinuous myoepithelial layer around nests of in situ lesions, and 2) they react with a small but significant subset of breast carcinoma tumour cells; however this aberrant reactivity rarely causes diagnostic difficulty. Relative to myofibroblasts, the specificity of p63 for myoepithelium is almost perfect. The authors conclude that p63, because of its near-perfect sensitivity and near-absolute specificity in distinguishing myoepithelial cells from myofibroblasts, represents a myoepithelial marker that can complement or replace SMM-HC and/or calponin in the analysis of microinvasion.

Detecting microinvasion can be difficult when there is a marked periductal fibrosis or inflammation because the true boundary of the specialized intralobular or periductal stroma is not clear but IHC for cytokeratin may be useful to confirm the presence of separate foci of neoplastic cells embedded in periductal fibrosis or inflammation.

Diagnosis of microinvasion sometimes remains problematic, even with the use of ancillary techniques. If there is sufficient doubt about the presence of microinvasion (i.e. in cases with marked fibrosis or inflammation) the case should be classified as in situ carcinoma/microinvasion possible as reported by the European Guidelines [22].

Differential Diagnosis

According to Fisher [28], microinvasion "represents one of, if not the most, commonly overdiagnosed events in the pathology of breast carcinoma".

A variety of patterns in DCIS and, more rarely, in LCIS, may be misinterpreted as stromal invasion. Schnitt [25] has

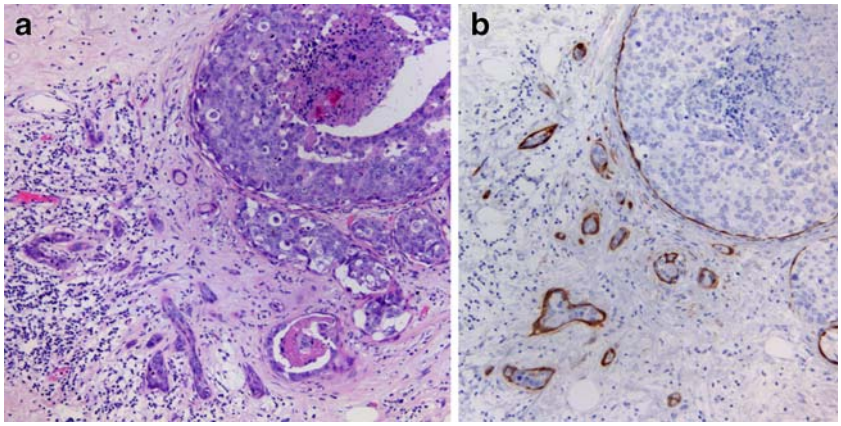

Fig. 3 **a** DCIS with lobular cancerization (H&E). **b** The same lesion shown in **a**, stained with SMM-HC confirms the presence of surrounding myoepithelial cells

summarized lesions and artefacts commonly mistaken for microinvasion:

1. DCIS involving lobules (lobular cancerization; Fig. 3a and b);
2. Chronic inflammatory reaction present in association with, and obscuring, involved ducts and acini (Fig. 4a and b);
3. branching of ducts;
4. distortion or entrapment of involved ducts or acini by fibrosis (due to prior needling procedure);
5. crush artefacts;
6. cautery effects;
7. artefactual displacement of DCIS or LCIS cells into the surrounding stroma or adipose tissue due to tissue manipulation or a prior needling procedure; in cases with a history of a prior needling procedure - fine needle aspiration cytology, needle core biopsy (NCB), vacuum assisted needle core biopsy (VANCB) - diagnosis of MC should be made with caution: artefactual disruption of the epithelial-stromal junction of glandular structures involved by in situ carcinoma is not infrequently encountered in subsequent excisional biopsy. Granulation tissue, old or recent haemorrhage, tissue tears, and a degenerative appearance of the dislodged tumour cells can help in distinguishing pseudo-invasion from true invasion [4];
8. DCIS or LCIS involving benign complex sclerosing lesions such as radial scar, sclerosing adenosis, sclerosing papilloma, ductal adenoma.

How to Avoid Underdiagnosis of Microinvasion

As reported above, microinvasion can be not only overdiagnosed but also underdiagnosed because the diagnosis depends principally on the tissue sampling. MC can not be reliably excluded unless all tissue is serially sectioned and sequentially submitted for histological examination. Serial macroscopic sectioning is estimated by some to be too expensive although a cost-effectiveness study of serial sectioning has never been performed to our knowledge. This method is now recommended in clinical guidelines [29] as well in breast screening programmes [30]. However it is well-known that even with a high number of paraffin blocks, only a part of the tissue is examined microscopically, and pathologists can not be absolutely certain that microinvasion is really absent.

Serial sections supported by IHC usually provide the best evidence of microinvasion. Care should be taken to obtain IHC early in the evaluation of suspected microinvasion before the sample has been sectioned excessively [23]. This can confirm microinvasion and contemporaneously exclude the possibility of larger invasive foci.

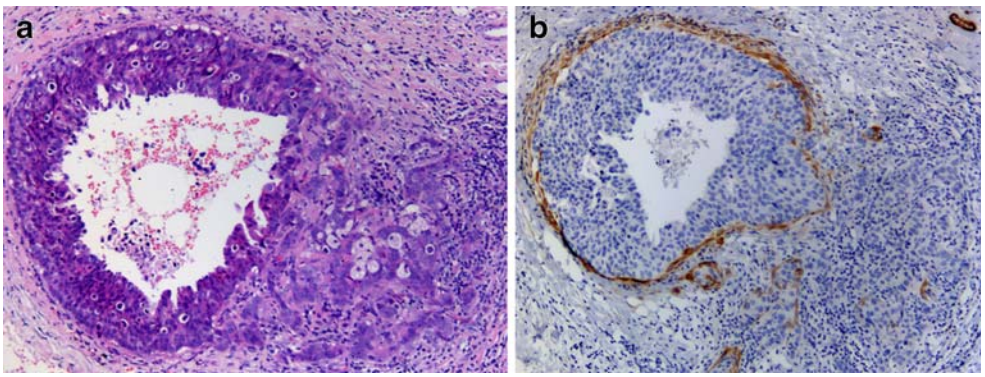

Fig. 4 **a** Microinvasive ductal carcinoma (H&E). **b** The same lesion shown in **a**, stained with SMM-HC confirms the absence of myoepithelial cells around tumour cell nests admixed with chronic inflammatory cells

Table 1 Review of literature: axillary lymph node status in microinvasive carcinoma according to different definitions of microinvasion

Study/reference number	Year published	Definition of microinvasion	No. of cases with axillary dissection or sentinel lymph node biopsy	No. of cases with positive axillary lymph nodes (%)
Schuh et al. [9]	1986	Foci of stromal invasion, maximum size not specified	30	6 (20)
Kinne et al. [31]	1989	Foci of stromal invasion, maximum size not specified	42	4 (9.5)
Patchefsky et al. [10]	1989	Stromal invasion in less or equal to 10% of surface of histologic sections examined	16	2 (12)
Wong et al. [11]	1990	Microscopic focus/i of malignant cells invading beyond the basement membrane as determined by light microscopy, maximum size not specified	33	0
Rosner et al. [15]	1991	Stromal invasion in less or equal to 10% of surface of histologic sections examined	34	1 (3)
Simpson et al. [32]	1992	Foci of stromal invasion, maximum size not specified	5	1 (20)
Solin et al. [16]	1992	Invasion less than or equal 2 mm or comprising less than 10% of the tumour	39	2 (5)
Silverstein et al. [33]	1997	1 focus or more foci, each less or equal to 1 mm	17	0
Aktar et al. [34]	1998	1 focus or more foci, each less or equal to 1 mm	25	0
Jimenez et al. [35]	1998	1 focus or more foci, each less than 1 mm	23	1 (4.3)
Silver et al. [17]	1998	1 focus less or equal to 2 mm or up to 3 foci, each less or equal to 1 mm	38	0
Le Bouedec et al. [36]	1999	1 focus less or equal to 2 mm or up to 3 foci, each less or equal to 1 mm	60	3 (5)
Mann et al. [37]	1999	1 focus or more foci, each less or equal to 1 mm	18	0
Zavotsky et al. [38]	1999	1 focus less or equal to 2 mm or up to 3 foci, each less or equal to 1 mm	14[a]	2 (14.3)
Klauber-DeMore et al. [39]	2000	1 focus or more foci, each less or equal to 1 mm	31[a]	3 (9.7)
Padmore et al. [40]	2000	1 focus or more foci, each less or equal to 1 mm	11	0
Prasad et al. [41]	2000	1 focus or more foci, each less or equal to 1 mm	15	2 (13.3)
Cox et al. [42]	2001	1 focus or more foci, each less than 1 mm	15[a]	3 (20)
De Mascarel et al. [18]	2002	Type 1: a few single infiltrating tumour cells (from 1 to 15)	59	0
		Type 2: a few infiltrating tumour cell clusters	139	14 (10.1)
Wasserberg et al. [43]	2002	1 focus or more foci, each less or equal to 1 mm	28	3 (10.7)
Wong et al. [44]	2002	1 focus or more foci, each less or equal to 1 mm	24[a]	2 (8.3)
Intra et al. [45]	2003	1 focus or more foci, each less or equal to 1 mm	41[a]	4 (9.7)
Yang et al. [46]	2003	1 focus or more foci, each less or equal to 1 mm	26	0
Buttarelli et al. [47]	2004	1 focus or more foci, each less or equal to 1 mm	11[a]	1 (9.1)
Giard et al. [48]	2005	1 focus or more foci, each less or equal to 1 mm	32[a]	1 (1.1)
Wilkie et al. [49]	2005	1 focus or more foci, each less than 1 mm	51[a]	7 (13.7)
Katz et al. [50]	2006	1 focus or more foci, each less or equal to 1 mm	21[a]	2 (9.5)
Leidenius et al. [51]	2006	1 focus or more foci, each less or equal to 1 mm	11[a]	1 (9.0)
Gray et al. [52]	2007	1 focus or more foci, each less or equal to 1 mm	81[a]	6 (7.4)
Le Bouedec et al. [53]	2007	1 focus or more foci, each less or equal to 1 mm	40[a]	4 (10%)
Zavagno et al. [54]	2007	1 focus or more foci, each less or equal to 1 mm	43[a]	4 (9.3)

[a] Series with sentinel lymph node biopsy

Clinical Significance of Microinvasion

Considering the variety of different definitions that have been used to report microinvasion and that some lesions categorized as MC based on limited tissue sampling could actually represent frankly invasive carcinomas, not submitted for histological examination or not represented on the slides because the cancer was deeper in the blocks, the clinical significance of microinvasion is still controversial.

Moreover the paucity and the non uniformity of the clinical outcome data has led to uncertainty regarding the separation of MC from in situ carcinomas on the one hand and, conversely, from small invasive carcinomas.

The current prevailing view is that MC appears to have an excellent prognosis with a low risk of associated axillary lymph node metastasis.

The reported incidence of axillary lymph node metastasis in patients given the diagnosis of MC ranges from 0% to

20% (9–11, 15–18, 31–54; Table 1). This wide range may be explained by both the different histopathological criteria used to define what constitutes microinvasion and the variable degrees of breast tissue sampling, but also it depends on the different techniques utilized to stain axillary lymph nodes (hematoxylin and eosin or IHC) especially after the introduction of sentinel lymph node (SLN) biopsy.

Although most clinicians have abandoned the routine use of SLN biopsy in all patients with in situ carcinoma (DCIS and pleomorphic LCIS), many still believe that there is a subset of patients with in situ carcinoma at high risk for MC and subsequent axillary metastasis who may benefit from the SLN biopsy procedure [50].

There is a general agreement, due to the significant rate of axillary metastasis in MC (Table 1), that SLN biopsy is a standard procedure in the treatment of patients with this type of lesion.

From a practical point of view, as microcalcifications considered to be associated with "in situ" breast carcinoma are preoperatively assessed by percutaneous NCB or VANCB, an accurate histological diagnosis identifying microinvasion on core biopsy allows the SLN biopsy and the excision of the primary tumour to be performed in a single surgical session.

Because of most of the MC with positive SLN have a low-volume metastases and consequently a low risk of additional metastases in axillary nodes, the role of complete axillary lymph node dissection is still debated.

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