E17. Ductal carcinoma *in situ* – an imaging challenge

Alexander Mundinger

Clinic of Radiology, Marienhospital, Johannisfreiheit 2–4, D-49074 Osnabrück, Germany

Abstract

Lobular carcinoma *in situ* (LCIS) is a marker of increased risk for later development of lobular or ductal invasive carcinomas. It presents with multifocal, multicentric and bilateral growth. Ductal carcinoma *in situ* (DCIS) is a heterogeneous precursor of later invasive carcinoma. It usually presents unilaterally, unifocally or multifocally and spreads within at least one segment. The frequency of necrosis and calcifications is highest in DCIS grade 3. Calcifications are the hallmark of DCIS in mammography. Instead of considerable categorical overlap, fine linear and linear branching calcifications suggest DCIS grade 3 with comedo necrosis. Pleomorphic (granular) calcification owing to necrosis suggests DCIS grade 2. Punctuate or amorphous flecks are typical for secretory calcifications in DCIS grade 1. Clustered calcifications represent cancerisation of the lobule, linear distribution reflects ductal spread. Linear distribution or segmental distribution of multiple calcified particles is more specific than morphology of a single particle. Detection rate of DCIS by ultrasound is low without knowledge of focal DCIS at mammography. By contrast, targeted ultrasound of suspected DCIS finds frequently hypoechoic lesions that are similar to small fibroadenoma, papilloma, ductectasia, microcyst or invasive cancer. Magnetic resonance imaging (MRI) diagnosis of DCIS affords high spatial resolution and is based on different interpretation criteria from those of invasive carcinoma. Clumped, linear, ductal and segmental enhancement is suspicious of DCIS even with slow or medium initial slopes and persistent late enhancement. Diagnostic accuracy is similar to mammography if used in pre-selected cases. Some DCIS do not enhance at all. To date, epidemiological data do not provide conclusive evidence that an aggressive diagnosis and treatment of DCIS leads to a decreasing breast-specific or overall mortality rate in comparison with a wait and watch strategy.

Background information

Definition

Intraductal carcinoma of the breast occurs as: (i) ductal carcinoma *in situ* (DCIS); (ii) an extensive intraductal component of an invasive ductal carcinoma; or (iii) pagetoid spread of cancer cells into the ducts of a lobular invasive carcinoma or a lobular carcinoma *in situ* (LCIS). The *in situ* carcinoma is defined as a clonal malignant proliferation that spreads only in pre-existent or newly formed acini, lobules and ducts and at the same time does not invade the adjacent intact basement membrane. Both entities can involve the acini of the lobules as well as the ducts, and the differentiation is sometimes difficult [1].

New insight into the polyclonal nature of usual ductal hyperplasia and the monoclonal lineage from progenitor cells over atypical ductal hyperplasia to DCIS stimulated a new World Health Organization (WHO) classification of ductal intraepithelial neoplasia (DIN). In concordance with Tavassoli and colleagues, increasing risk of invasion can be assumed for subsequent intraductal proliferations including heterogeneous DCIS [2] (Table 1).

Table 1. New World Health Organization (WHO) classification of ductal intraepithelial neoplasia (DIN) and assumed total cumulative risk of invasion

Old classification	WHO classification	Total cumulative risk of invasion (%)
Usual ductal hyperplasia	Usual ductal hyperplasia	–
Flat epithelial atypia	DIN, grade 1a	1–2
Atypical ductal hyperplasia	DIN, grade 1b	5–12
DCIS, low grade 1	DIN, grade 1c	10–32
DCIS, intermediate grade 2	DIN, grade 2	20–75
DCIS, high grade 3	DIN, grade 3	20–75

DCIS, ductal carcinoma *in situ*.

Clinical presentation of DCIS and LCIS

Today, most DCIS lesions are not palpable and are clinically unapparent. The Netherlands Cancer Institute reported an increase in asymptomatic DCIS from 47% to 77% between 1986 and 2002 following the nationwide introduction of mammographic screening [3]. The so-called special types of DCIS may display as a resistance (10% of all DCIS, intracystic papillary carcinoma or tumour-forming DCIS), a secretion (5–10% of all DCIS, apocrine papillary DCIS) or a mammilary eczema (<1% of all DCIS, Paget's disease). In contrast to DCIS, LCIS does not lead to clinical signs, symptoms or typical imaging features [4].

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Imaging challenge

Mammography

Most LCIS are detected as random findings during histological analysis of densities or microcalcifications. About 10–20% of DCIS lesions are mammographically occult. Eighty percent of DCIS present as microcalcifications mammographically, 10% show the feature of a spiculated lesion, 8% present as a focal mass, and 2% show intraductal changes at galactography. Microcalcifications with associated mass are found in 10% of mammographically visible DCIS lesions [5].

Depending on their extension, DCIS microcalcifications show a grouped, linear, segmental or, in advanced cases, regional or diffuse distribution. Granular, linear, branching and/or galactophoric topography of the microcalcifications is correlated with necrosis, grade 3, comedocarcinoma type. A number of microcalcifications higher than 20 is correlated with necrosis and grade 3 [6]. Evans and colleagues state that approximately 80% of calcific DCIS have an irregular cluster shape, and about 10% of these irregular clusters are V-shaped. Fifteen percent of all DCIS groups have an oval or round cluster shape. Mammographic and histological extension of DCIS corresponds highly in DCIS grade 3, and less in DCIS grades 2 and 1 due to mammographically invisible uncalcified tumour foci. In patients with DCIS a target zone of calcifications >1.5 cm is associated with a higher underestimation rate of infiltrating disease in comparison with a small group of calcifications. All suspicious calcifications of intermediate concern, and with higher probability of malignancy regardless of stability, should be biopsied; furthermore all suspiciously distributed microcalcifications, and all newly developing or progressive microcalcifications with irregular shape of cluster regardless of a benign appearing morphology of the single calcific particles should also be biopsied [7].

Ultrasound

Even in specialised centres, DCIS is rarely (<5%) predicted on the basis of ultrasound features alone. In the 1990s ultrasound equipment detected positive findings in mammographically positive DCIS in up to 40% of cases in our experience. To date several studies using modern ultrasound equipment report subtle findings of DCIS more frequently. Moon and colleagues performed targeted ultrasound using 10–13 MHz transducers in 1821 consecutive women with a suspicious mammographic or clinical abnormality or with newly diagnosed breast cancer before excision or percutaneous needle biopsy was performed. Thirty-three of these women had pure DCIS, 42 had DCIS with microinvasion and 519 had invasive carcinoma. The DCIS lesions manifested as a clinically occult mammographic lesion in 52 cases (74%), a palpable mass in 9 cases (13%), nipple discharge in 7 cases (10%), and an incidental ultrasound lesion in 2 cases (3%). The authors found an ultrasound correspondence of DCIS in 60–90% of cases. However, it is difficult to visualise a small cluster of calcifications without associated breast masses at ultrasound, particularly those less than 5 mm [8]. Yang and Tse retrospectively reviewed 60 DCIS lesions from 55 symptomatic women. 10% of the lesions were not visible on ultrasound, and 20% were not visible on mammography. Microcalcifications were detected on ultrasound in 22% of the 60 lesions or on mammography in 42% [4]. Nagashima and colleagues identified lesions associated with microcalcifications sonographically in 54 of 73 cases (74%) by using modern equipment [9]. Wilson and colleagues stated that the combination of high-frequency ultrasound with power Doppler is useful in the detection and guidance of successful needle biopsy of microcalcifications particularly where there is an invasive focus within larger areas of DCIS. Forty-one patients (93%) of their study had ultrasound abnormalities corresponding to mammographic calcification. Ultrasound-guided core biopsy was performed on 37 patients. Twenty-nine of 37 (78.4%) ultrasound-guided core biopsy obtained a definitive result [10]. To summarise the current experience with ultrasound of DCIS, most DCIS lesions without microcalcifications manifest as microlobulated (lobulations 1–2 mm in diameter), mildly hypoechogenic, lobulated or round mass with homogeneous echotexture and normal acoustic transmission. Spiculated margins, a thick echogenic rim and posterior acoustic shadowing suggest the presence of microinvasion. Microcalcifications resemble speckle echoes.

Magnetic resonance imaging

All magnetic resonance imaging (MRI) series published agree in the high sensitivity of breast MRI for detecting invasive breast cancers whereas the sensitivity varies from 45% to 85% in detecting DCIS. Most of these studies are retrospective, and included tumours with microinvasive and invasive components. In a study of Liberman and colleagues ductal enhancement accounted for 88 (21%) of 427 lesions and 88 (59%) of 150 no-mass lesions. Histological finding in these 88 lesions was DCIS in 18 (20%); infiltrating carcinoma in 5 (6%), including 3 with DCIS; and lobular carcinoma *in situ* (LCIS) in 9 (10%) [11]. Fischer and colleagues found an enhancement typical for malignancy in only 15 of 35 (43%) cases of DCIS at 1.5 T [12].

A segmental or a linear enhancement pattern was found for 50/1003 (5%) patients (17 DCIS, 33 benign breast diseases) by Morakkabati-Spitz and colleagues. Accordingly, the positive predictive value of segmental and

linear enhancement is 34% (17/50); the specificity of this criterion is 96% (826/859). For 4 of 24 patients (17%), DCIS was visible as segmental or linear enhancement on dynamic breast MRI, whereas no abnormalities were visible on the corresponding mammogram [13].

The majority of DCIS lesions shows clumped, linear (i.e. not surely nipple orientated), ductal or segmental enhancement at MRI. Mass enhancement is less common. Kinetic curves are not reliable if criteria of invasive carcinoma are used. Although there is a considerable overlap, DCIS grade 3 trends to enhance more intensely than low and intermediate grades. Differential diagnosis of ductal enhancement includes carcinoma (usually DCIS); atypical ductal hyperplasia; LCIS; and benign findings such as fibrocystic change, ductal hyperplasia, and fibrosis [11].

Limitations

With all imaging modalities, including positron emission tomography (PET), the actual pathohistological extension of DCIS will be underestimated. There is no imaging modality that can be used to visualise DCIS less than 5 mm in diameter, if the *in situ* cancer does not generate calcifications at mammography or enhancement at MRI. The positive predictive value of suspicious microcalcifications is poor at mammography. Sampled histological studies of more than 5000 cases after large core biopsy and stereotactic vacuum-assisted biopsies revealed that 14% of cases had DCIS and 10% had invasive carcinomas [14]. Thus in 76% of these cases microcalcifications have to be classified as false-positive in retrospect. The ultrasound appearance of hypoechoic DCIS lesion is frequently quite unspecific. Their differential diagnosis resembles several benign lesions like fibroadenoma and cystic disease. Up to now, epidemiological data do not provide conclusive evidence that an aggressive diagnosis and treatment of DCIS leads to a decreasing breast-specific or overall mortality rate in comparison with a wait and watch strategy [15].

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