Review

The diagnosis and management of pre-invasive breast disease

Radiological diagnosis

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Abstract

Pre-invasive disease is most frequently diagnosed in asymptomatic women following detection of microcalcification at mammography. The vast majority is ductal carcinoma *in situ*. This article summarizes the radiological features of pre-invasive disease and indicates which features are helpful in differentiating between benign and malignant conditions. The value of finding ductal carcinoma *in situ* at screening, predicting the presence of an invasive focus and methods of percutaneous biopsy of calcification are also addressed.

Keywords: calcification, diagnosis, ductal carcinoma *in situ*, mammography, screening

Introduction

Mammography is the primary imaging tool for the detection and diagnosis of ductal carcinoma *in situ* (DCIS). Other imaging techniques such as ultrasound, magnetic resonance imaging and scintimammography are insensitive in the absence of an invasive focus. Microcalcification is the commonest mammographic feature of DCIS and is seen in 80–90% of those cases with a mammographic abnormality [1]. However, the chance of symptomatic DCIS having a mammographic abnormality varies according to the clinical presentation. Virtually all cases of DCIS presenting with single duct nipple discharge have a mammographic abnormality, whereas only 50% of women with DCIS presenting as Paget's disease of the nipple have a mammographic abnormality [2].

Approximately 80% of cases of calcific DCIS have an irregular cluster shape and about 10% of these irregular clusters are 'V' shaped. The irregular cluster shape of DCIS is caused by the growth pattern of DCIS, which has a tendency to grow toward and away from the nipple within a single segment of the breast. One of the commonest and most characteristic features of DCIS is that the calcifications are aligned in a ductal distribution. This distribution is common in both necrotic and non-necrotic DCIS. If calcifications lack rod or branching shapes, then a ductal distribution can be extremely helpful in suggesting the presence of DCIS. Approximately 90% of DCIS calcification clusters have more than 10 flecks of calcification. However, diagnosing DCIS is not uncommon in lesions with clusters of five flecks or less.

The most common morphological features of calcifications due to DCIS are granular calcifications with irregularity in density, shape and size as compared with the other calcifications within the cluster. Although these features are present in over 90% of cases of DCIS, their usefulness in benign versus malignant differentiation is limited because these features are also commonly found in benign causes of calcification. The more specific features of DCIS such as a ductal distribution of calcifications, and rod and branching shapes are much less common, being found in 70%, 70% and 40% of cases, respectively. Punctate (round or oval) calcifications are also commonly found in DCIS. Just under 50% of DCIS calcification clusters contain punctate calcifications and 15% have predominantly punctate calcifications [3].

ADH = atypical ductal hyperplasia; ALH = atypical lobular hyperplasia; DCIS = ductal carcinoma *in situ*; FNAC = fine needle aspiration cytology; LCIS = lobular carcinoma *in situ*; VAM = vacuum assisted mammotomy.

A recent study [4] that examined previous mammograms of women with DCIS showed that in 22% the previous mammograms were, in retrospect, abnormal. The calcification morphology of the DCIS present on the previous mammograms was much less characteristic of malignancy than those present at the time of diagnosis. These cases, which had such nonspecific features at the time of previous mammography, were predominantly high-grade DCIS. This indicates that the characteristic morphological features of the calcifications in high-grade DCIS are frequently not present when the lesions are small.

In one recent study [5], by assessing and measuring mammographic calcification due to DCIS that was missed on previous mammography, the investigators were able to gain information concerning DCIS growth rates and growth directions. This study found that DCIS grows twice as fast in the nipple plane as in the plane at 90° to this. However, DCIS appears to grow at equal rates toward and away from the nipple. There appears to be a good correlation between both growth in the nipple plane and at 90° to the nipple with the cytonuclear grade of DCIS.

Atypical ductal hyperplasia (ADH), lobular carcinoma *in situ* (LCIS) and atypical lobular hyperplasia (ALH) can all manifest as mammographic calcification. They normally exhibit high-density, clustered punctate calcification and tend to lack the characteristic mammographic features of DCIS such a rod shapes, a ductal distribution and branching.

Appearance of ductal carcinoma *in situ* according to pathological subtype

The radiological appearances of DCIS vary markedly according to the pathological subtype. The following pathological variables have been shown to correlate with variations in the radiological appearance of DCIS: architectural pattern, cell size, necrosis, C-ebB-2 expression, P53 expression, MIB-1, and oestrogen receptor and progesterone receptor expression. Holland and coworkers [6] found that 80% of comedo DCIS had linear calcification but this finding was only present in 16% of cribriform/micropapillary DCIS. That study also found that only 53% of the cribriform DCIS group had mammographic calcification, as compared with 94% of the comedo group. In addition, the report shows that mammographic estimation of DCIS lesion size was more accurate in comedo DCIS than in the cribriform DCIS. Although other authors have confirmed that linear calcifications are more common in the comedo subtype of DCIS and that granular calcifications are more common in the cribriform/micropapillary types, it is impossible to predict reliably the architectural pattern of DCIS on mammography.

There are strong correlations between the presence or absence of necrosis and the mammographic features of DCIS. DCIS containing necrosis is more likely to show abnormal mammographic findings, calcification, calcification with a ductal distribution and rod shaped calcifications. DCIS without necrosis is more likely to show normal mammography, a noncalcific mass, or predominantly punctate calcification [1].

Post-conservation surveillance

Post-conservation surveillance mammography is especially important in women who have undergone wide local excision for treatment of DCIS because at least 50% of women with recurrent DCIS have invasive disease. Mammography is the sole method for detecting recurrent DCIS in the vast majority of these cases. A recent study of the mammographic features of locally recurrent DCIS demonstrated that 85% of local recurrences were detected solely by mammography and that 95% of recurrent DCIS was visible mammographically [7].

What is the value of detecting ductal carcinoma *in situ* at mammographic screening?

The introduction of mammographic screening has led to a dramatic increase in the number of cases of pure DCIS diagnosed. Of screen-detected breast cancers 25% are DCIS, as compared with 5% of symptomatic breast cancer [8,9]. Screening of women who are under 50 years of age identifies even higher proportions of DCIS lesions than are seen when screening women older than 50 years [10]. Critics of breast screening often claim that the high rates of DCIS seen represent over-diagnosis, many being lesions that would never present clinically and threaten the woman's life. This is compounded by the fact that such lesions may be extensive and therefore frequently require mastectomy to obtain adequate excision. Such criticism would be valid if screen-detected DCIS lesions were predominantly of low histological grade. However, DCIS detected by mammographic screening is predominantly of high nuclear grade and only 13% is low grade [11]. Screen-detected DCIS is also more likely to contain areas of necrosis than are symptomatic lesions.

The detection of high-grade DCIS by screening is likely to prevent the development of high-grade invasive cancer within a few years and could be important in producing part of the mortality reduction seen in randomized trials of mammographic screening. Approximately one-third of malignant calcification clusters contain an invasive focus. Recalling DCIS at screening is a good method of detecting small invasive cancers. Features that predict the presence of an invasive focus within DCIS are DCIS of high grade on core histology and increasing number of calcifications on mammography. High-grade DCIS on core and more than 40 calcifications on mammography indicates a 48% chance of occult invasion, whereas high-grade DCIS on core and fewer than 40 calcifications indicates a 15% risk for invasion. Lesions with non-high-grade DCIS on

core biopsy carry a very low risk for occult invasion [12]. There is a strong correlation between screening unit DCIS detection rates and their small invasive cancer detection rates [13]. The increased availability of stereotactic core biopsy with digital imaging should mean that an aggressive approach to mammographic calcification should not give rise to high rates of surgical benign biopsy [14].

ADH is a rare condition, being seen in only 4% of symptomatic benign biopsies. The incidence increases in association with screen-detected benign microcalcifications. The ability of mammography to detect microcalcification has thus resulted in an increase in the detection of ADH.

Percutaneous biopsy of pre-invasive disease

Microcalcifications are particularly difficult to biopsy as compared with mass lesions. This is true both for core biopsy and for fine needle aspiration cytology (FNAC). The absolute sensitivity of FNAC when biopsying microcalcification can be as high as 71% [15]. In general, however, the absolute sensitivity of FNAC in diagnosing DCIS is only in the region of 53% [16]. Although the lower absolute sensitivity of FNAC in the diagnosis of DCIS is of concern, the major issue when using FNAC in the diagnosis of microcalcification is the unreliability of FNAC to make a definitive diagnosis of benignity. In a series from Guildford, UK [15], 36% of indeterminate calcifications with C1 or C2 cytology were malignant. Stereotactically guided core biopsy of indeterminate calcification allows accurate diagnosis of the majority of microcalcification clusters. The ability to perform specimen radiography to confirm the presence of representative calcification within the specimens represents a significant advantage over fine-needle aspiration. The more recent widespread use of digital imaging has further enhanced the ability of stereotactic core biopsy to diagnose microcalcification accurately.

The introduction of digital stereotaxis has enabled the use of many more check pairs during a biopsy procedure. This allows very precise placement of the needle before firing and shortens the interval between obtaining an adequate position and firing; thus, the patient has less time to move out of position. With the introduction of digital stereotaxis our calcification retrieval rate immediately rose from 55% to 85%. Our absolute sensitivity for the diagnosis of pure DCIS rose from 34% to 69% and the complete sensitivity from 52% to 94% [13]. With further experience in the use of digital stereotaxis, our calcification retrieval rate for microcalcific lesions is now 96% and our absolute sensitivity for diagnosing pure DCIS is 81%. These figures indicate that the results of upright digital stereotaxis are similar to those achieved with prone table stereotactic biopsies. Acquiring specimen radiographs promptly is important when performing stereotactic core biopsies of microcalcifications. The use of digital imaging to provide immediate specimen radiography is very helpful because there is no delay between performing the biopsy and knowing whether the biopsy has been successful. It also means that if the specimen radiograph is negative then further cores can be taken without delay.

There is increasing absolute and complete sensitivity (absolute sensitivity is the percentage of B5 results from a malignant lesion, whereas complete sensitivity counts B3, B4 and B5 results as positive) with increasing number of cores, with six or more cores giving a better diagnostic yield than five cores [17]. These results highlight the frequent need to take multiple cores, and certainly 10–15 cores of microcalcification is not excessive. A recent study [18] aimed to determine whether the number of flecks of calcification retrieved with stereotactic needle core or the numbers of cores containing calcification were related to biopsy sensitivity. The investigators found that 100% complete sensitivity was obtained once three individual calcific flecks were obtained, but for 100% absolute sensitivity five or more flecks of calcification were required on specimen radiography. That study also showed that two of the cores showing at least one fleck of calcification was required for 100% complete sensitivity. For 100% absolute sensitivity, three separate cores each containing at least one fleck were required at specimen radiography. The other important finding of the study was that three specimen radiographs that contained only one or two flecks of calcification gave a benign result, even though the lesion was malignant on excision.

It has become clear that there are a number of cases in which image guided core biopsy significantly 'understages' malignant microcalcification. Most series indicate that approximately 50% of lesions with ADH on core show either DCIS or DCIS with invasive cancer at surgical excision [19]. Multiple studies have shown that approximately 20% of lesions giving a core biopsy result of DCIS have invasive disease at excision biopsy [20].

Percutaneous biopsy devices are now available that provide much larger volumes of tissue, and these can be used to reduce the need for diagnostic open surgical biopsy for benign conditions and to provide higher rates of preoperative diagnosis for malignant disease. Vacuum assisted mammotomy (VAM) retrieves multiple contiguous 14, 11 or 8 French gauge core samples by combining core biopsy with a vacuum system for both acquiring and retrieving tissue samples. VAM will under-stage disease less than half as often as will conventional core biopsy. The difference is particularly marked in the under-staging of DCIS. In a large review of core and VAM needle biopsies, DCIS was found at surgery following a biopsy result of ADH in 41% of core biopsies and only 15% of vacuum assisted samples. VAM underestimates the presence of invasive malignancy associated with DCIS in only 11%. A similar study found that VAM underestimated the pres-

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ence of invasive disease in half as many patients with DCIS as did core biopsy (10% versus 21%) and understaged DCIS in 19% as compared with 40% [21–23].

A number of studies have shown DCIS and invasive carcinoma following excision of lesions yielding ALH and LCIS at percutaneous biopsy [24–26]. The risk appears to be lowest for ALH and highest for pleomorphic LCIS with central necrosis and in lesions in which residual calcifications remain *in situ*. The majority of authors advise excision of calcific lesions with a core biopsy result of pleomorphic LCIS.

Conclusion

In conclusion, the detection, assessment and biopsy of DCIS remains a challenge but the benefits of detecting high grade DCIS and associated small invasive foci make it a worthwhile task.

Competing interests

None declared.

References

1. Evans A, Pinder S, Wilson R, Sibbering M, Poller D, Elston C, Ellis I: **Ductal carcinoma in situ of the breast: correlation between mammographic and pathologic findings.** *AJR Am J Roentgenol* 1994, **162:**1307-1311.
2. Ceccherini A, Evans AJ, Pinder SE, Wilson ARM, Ellis IO, Yeoman LJ: **Is ipsilateral mammography worthwhile in Paget's disease of the breast?** *Clin Radiol* 1996, **51:**35-38.
3. Evans AJ, Wilson ARM, Pinder SE, Ellis IO, Sibbering DM, Yeoman LJ: **Ductal carcinoma in situ: imaging, pathology and treatment.** *Imaging* 1994, **6:**171-184.
4. Evans AJ, Wilson ARM, Burrell HC, Ellis IO, Pinder SE: **Mammographic features of ductal carcinoma in situ (DCIS) present on previous mammography.** *Clin Radiol* 1999, **54:**644-649.
5. Thomson JZ, Evans AJ, Pinder SE, Burrell HC, Wilson ARM, Ellis IO: **Growth pattern of ductal carcinoma in situ (DCIS): a retrospective analysis based on mammographic findings.** *Br J Cancer* 2001, **85:**225-227.
6. Holland R, Hendriks JHCL, Vebeek ALM, Mravunac M, Schuurmans Stekhoven JH: **Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ.** *Lancet* 1990, **335:**519-522.
7. Liberman L, Van Zee KJ, Dershaw DD, Morris EA, Abramson AF, Samli B: **Mammographic features of local recurrence in women who have undergone breast-conserving therapy for ductal carcinoma in situ.** *AJR Am J Roentgenol* 1997, **168:**489-493.
8. Andersson I, Aspegren K, Janzon L, Landberg T, Lindholm K, Linell F, Ljungberg O, Ranstam J, Sigfusson B: **Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial.** *BMJ* 1988, **297:**943-948.
9. Smart C, Myers M, Gloecker L: **Implications from SEER data on breast cancer management.** *Cancer* 1978, **41:**787-789.
10. Evans WP, Starr AL, Bennos ES: **Comparison of the relative incidence of impalpable invasive beast carcinoma and ductal carcinoma in situ in cancers detected in patients older and younger than 50 years of age.** *Radiology* 1997, **204:**489-491.
11. Evans AJ, Pinder SE, Ellis IO, Wilson ARM: **Screen detected ductal carcinoma in situ (DCIS): over-diagnosis or an obligate precursor of invasive disease?** *J Med Screen* 2001, **8:**149-151.
12. Bagnall MJC, Evans AJ, Wilson ARM, Pinder SE, Denley H, Geraghty JG, Ellis IO: **Predicting invasion in mammographically detected microcalcification.** *Clin Radiol* 2001, **56:**828-832.
13. Evans A, Blanks R: **Should there be an upper limit for the detection of ductal carcinoma in situ (DCIS) at mammographic screening? An analysis using data from the UK NHS breast screening programme.** *Clin Radiol*, 2002, **57:**1086-1089.
14. Whitlock JP, Evans AJ, Burrell HC, Pinder SE, Ellis IO, Blamey RW, Wilson AR: **Digital imaging improves upright stereotactic core biopsy of mammographic microcalcifications.** *Clin Radiol* 2000, **55:**374-377.
15. Elliott AJ, Cooke JC, McKee G: **A 4-year retrospective analysis of screen detected and stereotactically biopsied microcalcification with emphasis on ways to reduce the number of benign biopsies.** *The Breast* 1996, **5:**410-414.
16. Venegas R, Rutgers JL, Cameron BL, Vargas H, Butler JA: **Fine needle aspiration cytology of breast ductal carcinoma in situ.** *Acta Cytol* 1994, **38:**136-143.
17. Rich PM, Michell MJ, Humphreys S, Howes GP, Nunnerley HB: **Stereotactic 14G core biopsy of non-palpable breast cancer: what is the relationship between the number of core samples taken and the sensitivity for detection of malignancy?** *Clin Radiol* 1999, **54:**384-389.
18. Bagnall MJC, Evans AJ, Wilson ARM, Burrell HC, Pinder SE, Ellis IO: **When have mammographic calcifications been adequately sampled at needle core biopsy?** *Clin Radiol* 2000, **55:**548-553.
19. Liberman L, Cohen MA, Dershaw DD, Abramson AF, Hann LE, Rosen PP: **Atypical ductal hyperplasia diagnosed at stereotaxic core biopsy of breast lesions: an indication for surgical biopsy.** *AJR Am J Roentgenol* 1995, **164:**1111-1113.
20. Liberman L, Dershaw DD, Rosen PP, Giess CS, Cohen MA, Abramson AF, Hann LE. **Stereotaxic core biopsy of breast carcinoma: accuracy at predicting invasion.** Radiology 1995, **194:**379-381.
21. Darling ML, Smith DN, Lester SC, Kaelin C, Selland DL, Denison CM, DiPiro PJ, Rose DI, Rhei E, Meyer JE: **Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large- core needle breast biopsy: results of surgical excision.** *AJR Am J Roentgenol* 2000, **175:**1341-1346.
22. Burak WE Jr, Owens KE, Tighe MB, Kemp L, Dinges SA, Hitchcock CL, Olsen J: **Vacuum-assisted stereotactic breast biopsy: histologic underestimation of malignant lesions.** *Arch Surg* 2000, **135:**700-703.
23. Brem R, Berndt V, Sanow L, Gatewood D: **Atypical ductal hyperplasia: histological underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-guage stereotactically guided directional vacuum-assisted biopsy.** *AJR Am J Roentgenol* 1999, **172**:1405-1407.
24. Georgian-Smith D, Lawton TJ: **Calcification of lobular carcinoma in situ of the breast.** *AJR Am J Roentgenol* 2001, **176:**1255-1259.
25. Shin SJ, Rosen PP: **Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy.** *Arch Pathol Lab Med* 2002, **126:**697-701.
26. Liberman L, Sama M, Susnik B, Rosen PP, LaTrenta LR, Morris EA, Abramson AF, Dershaw DD: **Lobular carcinoma in situ at percutaneous breast biopsy: surgical findings.** *AJR Am J Roengenol* 1999, **173:**291-299.

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