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ORIGINAL ARTICLE

Fine-needle aspiration cytology in nonpalpable mammographic abnormalities in breast cancer screening: results from the breast cancer screening programme in Oslo 1996–2001

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SUMMARY. Fine-needle aspiration cytology (FNAC) of nonpalpable mammographic lesions has been under attack from two sides for some years. There has been much discussion and controversy as to the ability to differentiate between in situ and invasive carcinomas in cytological material. A further issue is that of optimal sampling to obtain adequate cell material in sufficient quantity. We present the results of FNAC from 832 nonpalpable mammographic abnormalities detected in the course of the breast cancer screening programme in Oslo during 1996–2001. In 11.6% of cases the smears were inadequate, and there were 7% false negatives (FN) and 1.3% false positives. Of the FN, 64% represented microcalcifications and 86% were due to sampling errors. Absolute sensitivity was 74%, complete sensitivity 88% and specificity 88%. In 255 carcinomas a cytological diagnosis of them as in situ or invasive was made. In 93% of the invasive cases (190/205) these had been correctly identified as invasive on FNAC. In 78% of cases proper follow-up could be resolved by cytology/radiology alone. Suboptimal sampling and localization remains the main cause of FN FNAC results. Problems in differentiating between in situ and invasive breast carcinomas can be significantly reduced by applying strict criteria for in situ lesions.

Keywords: Fine-needle aspiration; Breast cancer screening; Nonpalpable lesion; DCIS; Breast carcinoma; Grid plate

INTRODUCTION

Fine-needle aspiration cytology (FNAC) of palpable breast tumours is a valuable investigational tool with two major purposes. On the one hand, it is used to confirm a benign or probably benign radiological and clinical diagnosis, thus avoiding unnecessary surgical intervention. Alternatively, we want to confirm radiological and/or clinically malignant or suspicious findings, enabling definitive surgery without preoperative histological confirmation. In palpable lesions, results of about 3–10%[1–4] of FNAC are equivocal or suspicious and need bioptic confirmation.

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In both organized and opportunistic mammography screening, most of the mammographic abnormalities are nonpalpable and sampling with imaging guidance is necessary. A substantial number of these will represent proliferative breast lesions with or without atypia[5,6] and ductal carcinoma in situ (DCIS). The cytological features of these entities are variably well characterized. The specificity of the cytological criteria for high-nuclear-grade DCIS (Fig. 1) is high, although the ability to recognize an additional invasive component is limited.[7–15] Experience with nonhigh-nuclear-grade DCIS (Fig. 2) is more limited[8,16] and can be difficult to distinguish from proliferative lesions with or without atypia.[17] There have been attempts to define invasion criteria.[9,10,18] The limited experience in most pathology departments in diagnosing these entities, together with the low specificity of some of the criteria, has led to the use of core needle biopsies instead of, or in addition to, FNAC in many institutions.

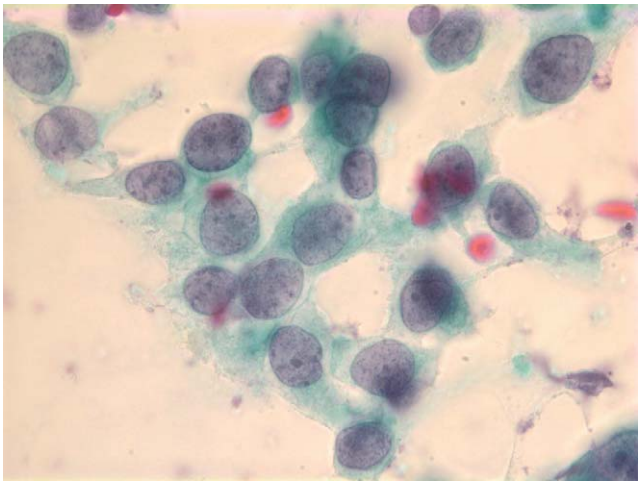

Fig. 1 Cells from a high-nuclear-grade DCIS. Original magnification × 100; PAP.

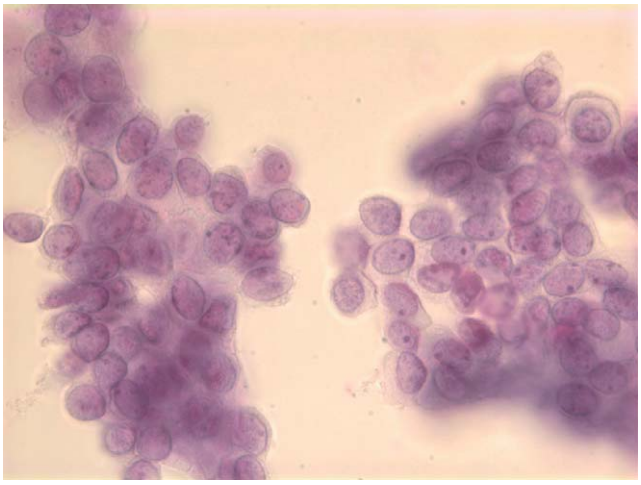

Fig. 2 Cells from a nonhigh (low)-nuclear-grade DCIS. Original magnification × 100; PAP.

Mammographic (mx) abnormalities that are not detectable on ultrasonography (US) can be aspirated using either a stereotactic (sx) device or a localization (grid) plate. The grid plate allows localization in two planes, whereas the depth of the lesions can only be roughly estimated. Owing to this limitation, many radiologists have abandoned the method and only use the sx device, which also allows accurate localization in the depth. The question of whether the results obtained with a grid plate differ significantly from those recorded with the sx device is still open. In our institution both methods are used.

The aim of this study was to evaluate the efficiency of imaging-guided FNAC in the diagnosis of nonpalpable mx and/or US-detected abnormalities.

MATERIALS AND METHODS

The material consisted of FNAC samples taken from 832 nonpalpable mx abnormalities found in the work-up of patients recalled in the breast cancer screening programme in Oslo during 1996–2001.

Pathologists performed all aspirations in close co-operation with the radiologists at the breast diagnosis centre (BDC). All nonpalpable lesions that were identifiable on US were aspirated with US guidance. Microcalcifications and other mx findings that could not be visualized on US were aspirated with the aid of an sx device or a localization (grid) plate. The radiologists decided which of the two methods was to be used in each case. Multifocal and/or larger lesions were usually aspirated with the aid of the grid plate, while the sx device was used in the case of small, single lesions. Core biopsies (CB) were not used. A total of 1–6 aspirations were performed in each case. One or more smears were stained with Diff-Quick (Dade AG, CH-3186 Dudingen, Switzerland) to ensure representative cell material and to make it possible to give a preliminary diagnosis to both the radiologist and the surgeon. The surgeon examined the women on the same day or the next. The radiological and the final cytological diagnoses were discussed in weekly multidisciplinary meetings to ensure optimal management of each woman. The management strategy is described in Table 1.

The cytological diagnostic categories used have been described previously.[12] All false-negative (FN) smears were reviewed by two of the authors (J.L. and K.Y.A.) to assess whether they were due to inadequate or suboptimal sampling or the result of interpretation errors. The size of each of the FN lesions was retrieved from the histopathology reports.

RESULTS

The results are given in detail in Tables 2 and 3. US guidance of aspiration was used for 41% of the lesions (215 + 122 cysts), the sx device in 21% (176) and the grid plate in 38% (319). In total there were 11.6% inadequate smears, 50 FN (7%) and 5 FP (1.3%).

All FP cases were seen during the first screening round. In three cases the lesions had not been marked preoperatively and no tumour was found in the surgical specimens. On review, the smears were still thought to indicate malignant lesions. In one case, a fibroadenoma with an extensive atypical intraductal hyperplasia (ADH) had been overdiagnosed. The last case had been cytologically diagnosed as DCIS, but histological examination showed only ADH.

Table 1 Management strategy and results

1. FNAC benign or inadequate/mx and US probably benign ⇒ back to screening (396 cases = 47.6%)/no histological confirmation necessary
2. FNAC benign or inadequate/mx and/or US equivocal, suspicious or malignant ⇒ diagnostic biopsy (108 cases = 13%)
3. FNAC equivocal or suspicious (irrespective of radiological diagnosis) ⇒ diagnostic biopsy (73 = 9%)
4. FNAC malignant (invasive or high-grade DCIS) (irrespective of radiological diagnosis) ⇒ therapeutic resection, including examination of the sentinel lymph node(s) (255 cases = 27.4%)

(DCIS, ductal carcinoma in situ; FNAC, fine-needle aspiration cytology; mx, mammography; US, ultrasound).

Table 2 Correlation between FNAC and histology of nonpalpable mammographic and/or US lesions

Histology	Cytology					
	Inadequate	Benign	Equivocal	Suspicious	In situ*	Invasive
None	34	240				
Benign	27	81	11	10		
ADH/ALH	5	14	5	14	3	2
DCIS	4	13	4	9	65	4
LCIS	2	1				1
Invasive	11	19	14	31	15	190
	86 (11.6%)					

*Includes papillary (in situ) carcinoma and high-nuclear-grade DCIS.
ADH, atypical intraductal hyperplasia; ALH, atypical lobular hyperplasia.

Table 3 Overview of image guided modalities with corresponding FNAC results

	US-guided	Sx	Grid	Total
Absolute sensitivity	79%	66%	69%	74%
Complete sensitivity	95%	77%	81%	88%
Specificity	93%	86.5%	85.7%	88%
FNR	5%	23%	19%	12.8%
FPR				1.6%
Inadequate rate	12%	23%	5.3%	11.6%

Sx, stereotactic localization; FNR, false-negative rate; FPR, false-positive rate.

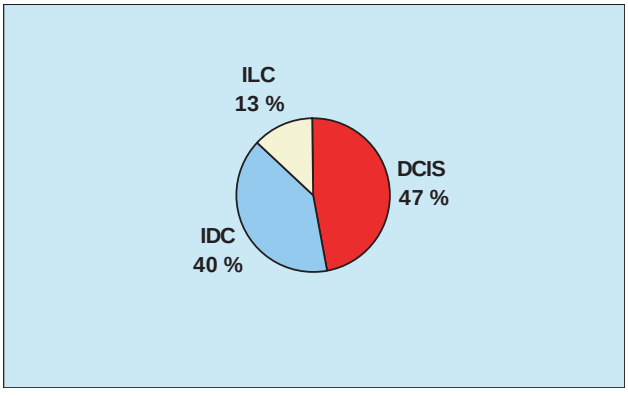

Fig. 3 Histological diagnoses of cases in which false-negative results of fine-needle aspiration cytology were recorded. (IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma).

The histological findings in FN lesions are shown in Fig. 3. Radiologically they represented microcalcifications (64%), tumours (26%), densities and distorsions. The mean and median diameters of 14 missed ductal carcinoma in situ (DCIS) and two missed lobular carcinoma in situ (LCIS) were 15.6 and 12 mm, respectively, ranging between 3 and 55 mm. In missed invasive carcinomas the mean and median diameters were 9.6 and 8 mm, respectively, with a range of 2–25 mm. Finally, there were four missed cases of DCIS with an additional invasive component. The mean diameters of the DCIS and the invasive components were 10.2 and 3.4 mm, respectively. On review, 86% of FN were found to be due to inadequate sampling and 14% to be interpretation errors. The interpretation errors were made in invasive G1 and G2 carcinomas in 80%, and in nonhigh-nuclear-grade DCIS in 20%.

In 396 cases (including the cysts), the cytological diagnoses were benign or the material was inadequate for diagnosis, whereas the radiological findings indicated a probably benign lesion (47.6% of all our cases). Two hundred and fifty-five carcinomas (27.4% of all cases) were correctly diagnosed as in situ or invasive. Of these, 93% of invasive cases (190/205) were correctly identified as such on FNAC. Thus, 78% of all cases could be resolved by cytology/radiology alone. In 66 cases (8%) both cytological and radiological findings were suspicious or equivocal, leading to a diagnostic biopsy; 74% of these were histologically borderline lesions, ductal carcinoma in situ or invasive carcinomas.

In 108 cases (13%) the radiological findings were suspicious or equivocal, whereas the cytological diagnoses were benign or inadequate. Histologically these lesions were benign in 72% of cases, whereas 28% were ultimately found to be in situ or invasive carcinomas.

DISCUSSION

High-quality FNAC practice includes localization/aspiration and interpretation as well as a multidisciplinary team approach. Suboptimal sampling and aspiration inevitably lower the sensitivity and specificity of FNAC, whereas the FN and inadequate rates will be higher than is desirable. In the UK breast screening programme about 30% of breast screening units achieved the targets for FN and inadequate rates,[19] demonstrating that localization and sampling/aspiration was a serious problem.

The main cause of FN FNAC in our material was microcalcification/DCIS with or without an additional invasive component. Most FNs were due to sampling errors (86%). A number of studies have yielded similar findings and led to the statement that microcalcifications, both benign and malignant/suspicious, are a major cause of inadequate cytological material.[20–22] Despite the high percentage of microcalcifications in the FN group, only 17% of DCIS were missed on cytology. They showed a broad range in size/extension from 3 mm and up to 55 mm. DCIS can be histologically both focal and extensive without being massive. DCIS may affect one or only a few ducts, but extend for several centimeters within these ducts, which explain why seemingly large DCIS lesions could be missed on cytology. Thus the main problem in targeting in situ lesions is the growth pattern of DCIS.

The interpretation errors were underdiagnosis of invasive carinomas G1/G2 (75%/25%) and DCIS G1 whose subtle atypia and/or specific criteria had been missed initially. The cytological criteria of low-nuclea-grade DCIS are less well documented in the literature than high-nuclear-grade DCIS. When the cell material is abundant the diagnosis can be made in most cases, but when the material is more scant and also contains clearly benign groups, diagnosis can be difficult. On review, and on comparison with histology, these cases were found to have sufficient cell material and cytological features consistent with the histological diagnoses. No high-nuclear-grade DCIS had been cytologically underdiagnosed.

Could we have diagnosed our FN FNAC by using CB in addition? In the UK breast screening programme the (mean) FN rate was higher for CB than for FNAC (13% vs 6.3%).[23] The (mean) inadequacy rate for CB was lower than that for FNAC (median 10.6%), and was slightly lower than the inadequacy rate for FNAC in our study. A recent study by Verkooijen et al.[24] reported 1.5% specimens that were inadequate for diagnosis and 4% FN in a series of 1029 large-core biopsies from nonpalpable mammographic lesions. Missed DCIS (16/20) accounted for 80% of their FN cases. Undoubtedly we could have picked up some of the FN cases by using CB in addition to FNAC, but not all of them. Small and/or focal lesions remain a localization problem irrespective of sampling modality.

Further comparison with the results obtained in the UK breast screening programme show that the absolute and complete sensitivity and also the specificity of FNAC in our study are higher than the (mean) corresponding values for CB in the UK.[23] Adding CB would most probably have only marginal effects on these parameters, while prolonging the time to definite diagnosis, and increasing the financial cost involved.

The cytological diagnosis of DCIS and the distinction between DCIS and invasive carcinoma has been the subject of much discussion and controversy in the cytological community and in the literature. Many pathologists remain reluctant to give a specific diagnosis of invasive vs in situ carcinoma. In our institution, we always try to differentiate between DCIS and invasive carcinoma. Key importance attaches to recognition of the specific features of high-nuclear-grade DCIS in a smear as a separate entity within the general cytological criteria of malignancy and to reporting this. The cytological criteria of high-nuclear-grade DCIS are well described in the literature. The diagnostic triad consists of highly atypical carcinoma cells found in groups and/or as single cells, comedo type necrosis and amorphous microcalcifications.[8] When these criteria are identified in a smear, we record a diagnosis of 'high-nuclear-grade DCIS, cannot evaluate invasiveness'. The question is not whether the cells represent DCIS or an invasive carcinoma, but whether there is an invasive component in addition to DCIS. An additional invasive component can be identified when fragments of fat or connective tissue show clearly invasive groups and/or single carcinoma cells.[9,10] Bonzanini et al.[11] were not able to demonstrate any difference between pure DCIS and DCIS with microinvasion, as would be expected. Studies describing criteria of invasion were published during the period in which our study material was diagnosed. Therefore, we do not know whether any, and if so how many, of the smears from the 15 DCIS (15/80 = 18.7%) (Table 2) with an invasive component contain fat or connective tissue fragments with infiltrating carcinoma cells or other invasion criteria that would allow a definite diagnosis of invasiveness. (This will be one of the subjects in a future study of our DCIS material.) Large-core biopsies do not solve this problem. Verkooijen et al.[24] reported 18% of 'upgrading' from DCIS to invasive carcinoma, which is completely in keeping with our FNAC findings.

Since the advent of the sentinel lymph node technique in breast cancer surgery, the distinction between invasive and high-nuclear-grade DCIS is not necessarily critical, as removal of the sentinel node(s) might be justified in both groups.[25] Primary surgery in the breast depends on the US and/or mx size/extension of the lesions, and not on whether they are invasive, microinvasive or pure high-nuclear-grade DCIS.[25]

The cytological criteria of nonhigh-grade DCIS and proliferative breast disease (PBD) with or without atypia overlap, and such findings always require a bioptic confirmation. The suspicious/equivocal cytological diagnoses (98 = 9%) reflect findings indicating nonhigh-grade DCIS, PBD with and without atypia and also cases with scant, but atypical cell material suspicious of (invasive) carcinoma. As almost half of the cases (Table 2) were diagnosed as invasive carcinoma on histology (45/98), the diagnostic problem of nonhigh-grade DCIS/PBD affects a small number of cases.

Experience and proper training of cytopathologists is essential to ensure that they will not only be able to recognize the specific features of high-nuclear-grade DCIS, but also be familiar with the characteristic features of low-nuclear-grade carcinomas, especially those of the tubular type. Failure to diagnose the majority of these will result in an unacceptably high FN interpretation rate. Low-grade invasive and nonhigh-nuclear-grade DCIS were the main causes of FN interpretations in our material.

The grid plate results compared favourably with the stereotactic (sx) results (Table 3). Sx-guided FNAC had the lowest sensitivity and specificity, and also the highest rates of insufficiency and FN. This does not mean that the method is inferior to the grid plate method, but primarily reflects the fact that it was used for the smallest and most difficult mx abnormalities. The grid plate is an acceptable method for larger and multiple lesions. It is also quicker than sx-guided FNAC and thus allows savings in terms of time and cost. Both methods miss some of the DCIS and invasive carcinomas, and a benign or inadequate cytological diagnosis in conjunction with unclear mx abnormalities always requires a diagnostic biopsy.

The close cooperation between radiologist and pathologist in the BDC practised at our institution is mutually rewarding. We make our cytological diagnoses in full knowledge of the radiological findings. Discussions on site enable immediate feedback on both cytological and radiological findings. Discrepancies are discussed. When indicated, the aspiration can be repeated, if appropriate using another modality. The combined cytological and radiological findings enabled a definitive management plan for the patients concerned (definitive surgery for invasive or in situ carcinoma or return to the regular screening programme) in 78% of the recalls.

In conclusion, suboptimal sampling and localization remain the main cause of FN FNAC results. Problems in differentiating in situ and invasive breast carcinomas can be significantly reduced by applying strict criteria for in situ lesions.

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