The role of fine needle aspiration cytology in the diagnosis of breast lesions

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Fine needle aspiration of breast lesions is widely practised as a simple, non-invasive procedure in hospital and private practice settings. Although the procedure is liable to sampling error—especially when the lesion is very small and non-palpable and variations may occur during the interpretation by different cytopathologists—it is a useful and important means of providing pre-operative diagnosis for women with abnormalities of the breast detected either by palpation or by imaging. We review the current status of this procedure and experience at our hospital.

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Introduction

In Hong Kong, breast cancer ranks as the second most frequent cancer among women (by crude incidence rate). There were 1106 new cases of breast cancer in 1991 with 333 deaths, of which 315 cases (28.5%) were in women aged between 31 to 44 years.[1] In 1993, there were 313 deaths from breast cancer of which 97 deaths occurred in women younger than 50 years. The mortality rate was 10.8 per 100 000 population.[1] The increase in incidence among younger women calls for the early detection of this disease. Palpable lesions may be detected by the patient or by a clinician. Non-palpable lesions are identified through the screening of high-risk groups and elderly women. The former includes those with a family history of breast cancer or patients who have had breast cancer. The radiologist plays an important role in the regular screening of women by mammography and ultrasound. Both needle core biopsy and fine needle aspiration cytology (FNAC) have been used successfully for pre-operative diagnosis in many cases and unnecessary operations have been avoided as a consequence.

Needle core biopsy is a form of biopsy where a piece of tissue is cut and becomes lodged in the lumen of the needle in the form of a solid core of tissue. Although the architecture of the breast lesion is maintained and the cellular pattern is preserved, core biopsy is usually more traumatic than is FNAC and may cause bleeding. In addition, it is not ideal for small and/or hard lesions which are difficult to locate or biopsy. Fine needle aspiration cytology is a simpler and less invasive procedure where cells (sometimes with accompanying stromal tissue) are dislodged into the needle. Sampling of the appropriate site may be facilitated by ultrasound guidance and/or mammographic localisation.[2,3] Direct smear and cell block (or Cytospin) are prepared and examined for cytological evidence of malignancy (Fig 1).

Fig 1. Fine needle aspirate specimen of tubular carcinoma. Note the dehiscence of tumour cells which contain moderate amounts of cytoplasm and darkly-stained nuclei, some are arranged in tubules (x 500)

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Fine needle aspiration cytology of breast lesions has been widely practised and is well-regarded.[4] It may be used as a preliminary diagnostic procedure, as a screening procedure with or without ultrasound or stereotactic guidance,[5] or as a follow up procedure post-mastectomy or -lumpectomy.[6]

We report here the past 10 years' experience of FNAC in the diagnosis of benign and malignant breast lesions at our institution.

Materials and methods

The cytological material used in this study of breast lesions came from one of three sources—surgeons, radiologists, or the cytopathologists who performed the procedure in a specialised clinic.

For FNAC, a 23–gauge needle, a 10 ml syringe and a Cameco (Cameco AB, Taby, Sweden) or Inrad (Inrad, Grand Rapids, Mi, US) needle holder were used to perform the aspiration on palpable lesions. Preferably, a direct smear was made on albuminised slides which were spray-fixed or fixed in 95% alcohol for at least 30 minutes (or overnight). The syringe was rinsed in 10 ml of 50% saline alcohol with smears subsequently prepared, or in 10% buffered formalin for cell block preparation. On occasions when help from an assistant was not readily available, the aspirate was simply flushed into fixative for later smear production. When the cellularity was low, a more cellular concentrate was prepared using the Cytospin method.[7,8] For nipple discharge, direct imprint smears were made.

Results

In the ten years from January 1985 through December 1994, there were 2914 breast cytology cases (including nipple discharge) from 2146 patients. Subsequent biopsy confirmation was available in 1330 cases. Cases with insufficient material were excluded (Table).

The diagnostic categories used in FNAC of the breast include the following: inadequate, benign, equivocal or atypia, suspicious of malignancy, and malignant. An inadequate sample refers to one with scanty epithelial cells which are probably not representative of the lesion, or to smears which are technically suboptimal for assessment. The inadequacy rate varies from institution to institution and is usually lowest when only a few individuals are assigned to perform the aspiration. The rate is lower for image-guided FNAC of a palpable lesion and is higher for non-palpable lesions. At the Prince of Wales Hospital, the average inadequate rate was 25% (717 cases) [95% CI, 23% to 26%]. The figure was highest in 1989 (37%) and decreased in 1994 (17%) following the introduction of image-guided fine needle aspiration and a fine needle aspiration clinic where the FNAC was performed by pathologists.

A benign diagnosis is given when there is an adequate sample of benign epithelial cells with no evidence of malignancy. In most circumstances, categorisation into specific pathological entities such as cyst, fibroadenoma (Figs 2a and 2b), or fibrocystic disease is possible. In general, the diagnostic accuracy for benign lesion is more than 95%[4]; in our hospital, the diagnostic accuracy for benign lesion reached 95% [95% CI, 93% to 97%].

An equivocal or atypia diagnosis is given when although the overall pattern of the aspirate is benign, there is a population of cells which show either loss of cohesiveness and/or nuclear pleomorphism and where the possibility of malignancy cannot be entirely excluded.[9] In our series, 2.5% of aspirates from benign lesions exhibited atypical features and 6.9% of aspirates from malignant lesions were classified likewise because of the lack of definite features of malignancy yet the presence of atypical cells. With the increased detection of atypical epithelial hyperplasia in lumpectomy specimens—these indicate a higher risk

Table. Correlation of cytology and histology results for cases of breast lesion at the Prince of Wales Hospital from January 1985 through December 1994

Histology		Cytology -benign	Cytology -atypia	Cytology - suggestive of tumour	Cytology -malignant
Benign	609	576	15	16	2
Malignant	464	37	32	92	303

* Cases with insufficient material were excluded from this correlation table.
False negative rate = 8%; false positive rate = 0.3%; diagnostic accuracy for benign lesions = 576/609 x 100 = 95%; diagnostic accuracy for malignant lesions (including atypia) = 427/465 x 100 = 92%.

Fig 2a. Fine needle aspiration cytology of a fibroadenoma. The epithelial cells form cohesive sheets in a staghorn configuration with scanty cytoplasm. Scattered naked nuclei are seen in the background. The inset shows a tiny fragment of fibromyxoid stroma (x 50)

Fig 2b. Subsequent excisional specimen of fibroadenoma (x 50)

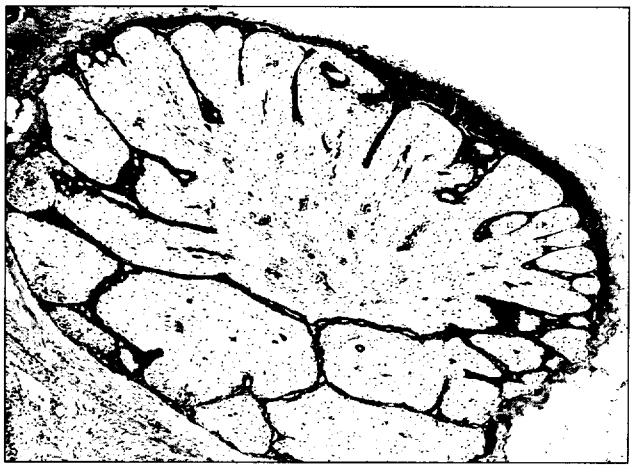

Fig 3. Infiltrating lobular carcinoma (x 125). At the inset, fine needle aspiration cytology of the tumour showing oval hyperchromatic cells and Indian filing (x 250)

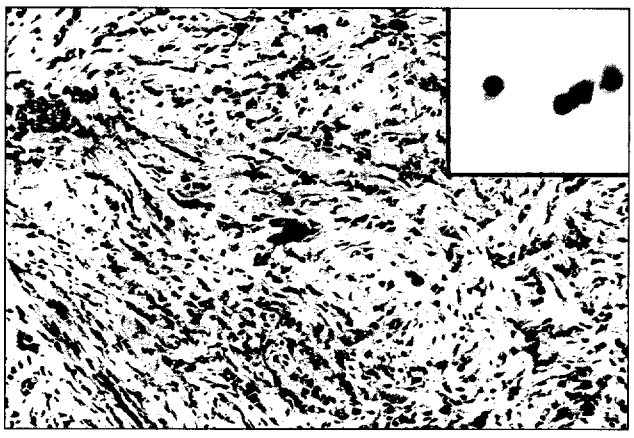

Fig 4. Fine needle aspiration cytology of ductal carcinoma. Note the pleomorphic nuclei and prominent nucleoli (x 500)

of developing cancer (five-fold increased risk)—the FNAC will help to uncover these high-risk lesions at an earlier stage.[10] When our accumulated experience was limited (for instance, at the beginning of the establishment of the FNAC service), cases were more often classified as equivocal. With the increased experience of the cytopathologists and co-operation with the clinicians and radiologists, the number of cases in this category has decreased. With this diagnosis, further investigation via an excisional biopsy is usually indicated.

A diagnosis that is suspicious of malignancy usually refers to samples that contain cells with only some features of malignancy, or a sample with only a scanty number of abnormal cells, or poorly preserved but abnormal cells. The reported range for this diagnostic group is from 7% to 20%.[9,11] The frequency is related to the nature of the sample, the experience of the cytopathologist, and the histology of the lesion.[12] For instance, tubular carcinoma, lobular carcinoma (Fig 3), mucinous carcinoma, and papillary carcinoma usually contain monotonous cells and uniform nuclei which are often under-diagnosed and result in "false negative" cases.[13-17]

A malignant diagnosis is made when there is sufficient number (based on the cellularity) of well-preserved cells with malignant features (Fig 4). The positive predictive value of malignancy should be greater than 95% with a false positive rate of less than 1% and false negative rate of less than 5%. At the Prince of Wales Hospital, our diagnostic accuracy rate was 92% [95% CI, 90% to 94%] for malignant lesions, which included 7% of cases diagnosed as atypia. Features leading to over-diagnosis include pregnancy change (nuclear atypia), epithelial hyperplasia in fibroadeno-

ma, and fibrocystic disease, papilloma, cystosarcoma phyllodes, and gynaecomastia in men.[18,11] In many cases, over-diagnosis can be avoided if the pathologist is provided with the relevant clinical information.

For under-diagnosed cases, the false negative rate ranges from 1% to 31% and is mostly attributed to sampling error.[19] Other causes include small tumour size (< 1 cm in diameter) [especially in clinically occult lesions detected by imaging], scirrhous lesions, post-irradiation fibrosis, and tumour necrosis. For the study period, our false positive rate was 0.3%, and the false negative rate was 8%. The predictive value for benign lesions and malignant lesions were 94% [95% CI, 92% to 96%] and 93% [95% CI, 90% to 95%], respectively. The sensitivity of FNAC was 95% [95% CI, 92% to 96%], and the specificity was 93% [95% CI, 89% to 94%].

Discussion

Fine needle aspiration cytology is now regarded as the method of choice in the preliminary investigation of breast lesions. The advantages of FNAC include the simplicity of the method, which is well-tolerated by patients, and the high diagnostic rate achieved, especially in small (but not < 1 cm) and/or hard lesions. A disadvantage is the lack of architectural information that is provided by needle core biopsy. Hence, the interpretation of FNAC requires more training and experience than does the reading of a needle core biopsy.

The diagnosis of breast lesions requires a triple approach—the cytology should be correlated with the clinical findings and imaging results as all of these are mandatory for the responsible management of the patient. An important component of reporting FNAC is to establish a common dialogue with the clinicians involved. The categories quoted above are well-established and easy to follow. Regular meetings with the surgeons, radiologists, and oncologists provide a chance for discussion with input from the various specialties managing the patient. Feedback is particularly important for atypia cases. Referral of FNAC of the breast to a small group of cytopathologists who are interested in this field would help to improve the diagnostic rate through constant training and the increased experience of those involved.

Apart from the common diagnoses of benign lesions (such as fibroadenomas, fibrocystic change, and inflammatory conditions) and carcinomas, FNAC has been reported to be useful in the diagnosis of uncommon conditions such as mycoses, malacoplakia, Rosai-Dorfman disease, adenomyoepithelioma, metaplastic carcinoma, secretory carcinoma, lipid-secreting carcinoma, mucoepidermoid carcinoma, carcinoid tumour, and mesenchymal tumours.[20-28]

Metastatic tumours in the breast diagnosed by FNAC include primaries from the lung and thyroid, lymphoma, soft tissue tumours, carcinoid tumour from an ileal primary and choriocarcinoma.[29-33] Granulocytic sarcoma and myeloid metaplasia diagnosed by FNAC have also been reported.[34] Fine needle aspiration cytology is also used to diagnose lesions of male breasts such as gynaecomastia and carcinoma, accessory axillary breasts and their lesions, and the status of axillary lymph nodes.[35,36]

Certain pitfalls should be borne in mind when performing FNAC on breast lesions. Aspiration should be repeated after aspiration of breast cysts, especially if there is a residual mass, as malignancy may be masked by the presence of cystic degeneration or necrosis.[37] Malignancy may also be masked by the presence of infection and inflammation.[38] Mammography should be avoided until three weeks after the performance of a fine needle aspiration or biopsy as it may lead to difficulties in interpretation.

Fine needle aspiration cytology has progressed beyond being a diagnostic procedure. Hormonal receptor (oestrogen and progesterone) estimation, with or without the help of image analyser, are now performed with results which correlate well with subsequent biochemical assays of tumour tissue.[39-41] Flow cytometry is also useful as an adjunct in doubtful cases as malignant cells are usually associated with aneuploidy.[42] Tumour marker immunohistochemistry assays which may be used include carcinoembryonic antigen, c-erbB-2 and neu oncoproteins, p53 protein, Ki67 growth fraction and pS2 protein.[43-47] Specific tumour markers such as keratin 19 (K19) transcripts and B72.3 antibody have been reported to be useful in the detection of carcinoma cells including those present in marrow aspirates in cases of occult metastasis to the bone.[48,49]

The use of prognostic markers such as epidermal growth factor receptor, proliferating cell nuclear antigen and vimentin have also been based on the immunohistochemistry of aspirated material.[50] Finally, the utilisation of an interactive computer system and digital image analysis which evaluates, diagnoses, and determines prognosis based on cytologic features derived from a digital scan of fine needle aspirate slides has been reported.[51] This has great potential for improving the evaluation of breast disease.

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