

# Fine needle aspiration cytology of breast masses: an evaluation of its accuracy and reasons for diagnostic failure

JANMEJAY J PATEL  
Medical Student

PAUL C GARTELL FRCS  
Senior Surgical Registrar

JAMES A SMALLWOOD FRCS  
Lecturer in Surgery

AMANDA HERBERT MRC PATH  
Consultant Pathologist  
Southampton General Hospital

GAVIN T ROYLE MS FRCS  
Senior Lecturer in Surgery

ROGER BUCHANAN MRCP (UK) FRCR  
Consultant Radiotherapist

IRVING TAYLOR MD ChM FRCS  
Professor of Surgery

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## Summary

A study of 1458 patients who had undergone breast aspiration cytology was conducted to determine the diagnostic accuracy of the technique. The effect of tumour histology and size on the unsatisfactory aspirate and false negative rate was examined. Seven hundred and thirty one patients (50%) had histological diagnoses. The sensitivity of aspiration cytology for malignancy was 64% for the first aspiration, but was 91% in patients who had had 3 aspirates. The specificity was 56%, this low figure was almost entirely due to inadequate or unsatisfactory cytological preparations. The positive and negative predictive values of aspiration cytology were 99.4% and 85% respectively demonstrating high diagnostic accuracy given a satisfactory aspirate. Invasive lobular carcinoma yielded a significantly higher unsatisfactory rate than invasive ductal carcinoma ( $P < 0.001$ ) and fibroadenoma yielded a significantly lower unsatisfactory rate than fibroadenosis ( $P < 0.001$ ). Mass size influenced the unsatisfactory rate for invasive ductal carcinoma ( $P < 0.05$ ) and fibroadenoma, but not for invasive lobular carcinoma or fibroadenosis. Only 2 of the 32 false negatives were due to misinterpretation, the remainder resulted from the aspiration needle missing the mass. We conclude that aspiration cytology is an accurate preoperative diagnostic procedure for the evaluation of breast masses. Unsatisfactory or negative aspirates should be regarded as 'non-results' if there is clinical or radiological suspicion of malignancy.

## Introduction

Clinical examination, fine needle aspiration cytology and breast radiology comprise an accurate triple assessment scheme for the preoperative evaluation of breast masses (1-5). Although aspiration cytology is a well accepted

diagnostic procedure with many advantages to favour its use (6-12), it may yield an equivocal result (13,14). This leads to problems for the patient and clinician. Extra time and resources are required and the patient may have to face the psychological morbidity of waiting for repeat aspiration, Tru-cut<sup>®</sup> needle biopsy and/or frozen section prior to definitive treatment.

Diagnostic failure of aspiration cytology has been attributed to a high unsatisfactory aspirate rate (15). This may be due to either insufficient epithelial cells being present, equivocal smears or unrepresentative aspirates resulting in false negative diagnoses (16).

This paper reports the results of aspiration cytology since its inception in the Southampton Breast Clinic in July 1981 and examines the reasons for diagnostic failure.

## Patients and methods

The study included 1458 patients who attended the breast clinic between July 1981 and November 1985. A total of 1663 aspiration cytologies were performed on these patients and 731 had subsequent excision of the breast mass providing a histological diagnosis.

Fine needle aspiration cytology was performed using a 23 gauge needle attached to a disposable 20 ml syringe mounted on a Cameco type syringe piston holder. All aspiration cytologies were performed by clinicians consulting at the Breast Clinic.

The aspirated material was expressed onto microscope slides for smearing, which was performed with a cover slip by a cytotechnologist. The aspirate was air dried and stained with May Grunewald Giemsa.

The cytology was reported as malignant, benign, equivocal or unsatisfactory. Aspirates with insufficient numbers of epithelial cells to reach a diagnosis were reported as unsatisfactory. The cytologic diagnoses from satisfactory aspirates were scored on a five point scale.

Correspondence to: Professor Irving Taylor, University Surgical Unit, University of Southampton, Level F, Centre Block, Southampton General Hospital, Tremona Road, Southampton.

- 2 - Definitely benign
- 1 - Probably benign
- 0 - Equivocal
- +1 - Probably malignant
- +2 - Definitely malignant

Cytologic diagnoses were compared with histologic diagnoses where available. The histopathology and size of lesions that yielded unsatisfactory and false negative aspirates were determined and a detailed analysis performed. All results were analysed by simple significance testing and the accuracy of aspiration cytology was assessed by the following:

**Sensitivity** Ratio of the number of +1 or +2 cytology results to the total number of masses diagnosed histologically as carcinoma

**Specificity** Ratio of the number of -1 or -2 cytology results to the total number of masses diagnosed histologically as non-carcinoma.

**Positive predictive value** Probability that mass actually is carcinoma when result of aspiration cytology is positive (+1 or +2)

**Negative predictive value** Probability that mass actually is benign when the result of aspiration cytology is negative (-1 or -2)

**Diagnostic accuracy** Overall proportion of correct diagnoses made by aspiration cytology.

**Results**

The median age of the 1458 patients was 51.5 years (range 14-94) with little variation annually. The number of aspiration cytologies performed per year increased steadily (Table I).

TABLE I. Number of aspiration cytologies performed per patient

Year	Number of patients	Number of patients with			Total cytologies
		one cytology	two cytologies	three cytologies	
1981	89	89	0	0	89
1982	247	232	14	1	263
1983	303	256	35	12	362
1984	420	378	32	10	472
1985	399	337	46	16	477
Total	1458	1292 (88.6%)	127 (8.7%)	39 (2.7%)	1663

The proportion of different cytologic diagnoses is shown in Table II. The overall unsatisfactory aspirate rate was 41.6%, but there has been a significant improvement since aspiration cytology was first introduced in Southampton.

Histological diagnoses were available for 731 patients. The number and proportion of false negative and false positive cytologic diagnoses for the periods 1981-1983 and 1984-1985 is shown in Table III.

Review of the 32 false negative cases confirmed the benign nature of 25 aspirates, but 4 of these did contain

TABLE III. False negative and false positive diagnoses per year

Year	Number of patients with histology available	Number false negative	Number false positive
1981-3	393	14 (4%)	2 (0.5%)
1984-5	338	18 (5%)	0 (0%)
Total	731	32 (4%)	2 (0.3%)

TABLE IV. Sensitivity of aspiration cytology on first, second and third aspirations: total malignant masses=427

Aspiration	No. with malignant masses	No. correctly identified	Sensitivity
First	427	274	64.2%
Second	58	25	43.1%
Third	25	14	56.0%
Overall	427	313	73.3%

atypical ductal cells. A further 5 aspirates had very few breast cells and were considered on review to be unsatisfactory for diagnosis. The remaining 2 aspirates were considered, in retrospect, to contain probable well differentiated carcinoma cells, which could have merited an equivocal rather than a negative score.

There were two false positive diagnoses in the series. The first was diagnosed as probably malignant with a score of +1 on the Southampton scheme. Histology of the mass revealed a tiny focus of duct papillomatosis and an area of necrosis. Doubt remains as to whether this was representative, as a proportion of the mass was submitted for oestrogen receptors and was therefore unavailable for histological diagnosis. The finding of positive oestrogen receptors in this patient may indicate that a small tumour was present. The second false positive was diagnosed as malignant on cytology by an inexperienced cytologist, based on only a few cells.

A total of 427 breast malignancies had histological diagnoses and 274 (64%) were positively diagnosed by the first aspiration cytology (Table IV). Second and third aspirations had a sensitivity of 43% and 56% respectively.

The overall sensitivity of aspiration cytology for malignancy was 73.3% (313 of 427 patients), however extrapolation from Table IV shows a cumulative sensitivity of 91% for malignancy after 3 aspirations.

One hundred and eighty out of 304 benign breast masses yielded benign cytology, a specificity of 59.2% if unsatisfactory aspirates are included in the calculation. Malignant masses were correctly identified in 313 of 315 patients who had positive aspiration cytology, with 2 false positives, giving a predictive value of 99.4% for malignancy. Benign masses were correctly identified in 180 out of 212 patients who had benign aspiration cyto-

TABLE II. Fine needle aspiration cytology of breast masses in Southampton: cytologic diagnosis per year (1981-1985)

Year	No. of cytologies	No. malignant	No. benign	No. equivocal	No. unsatisfactory
1981	89	15 (16.9%)	31 (34.8%)	0 (0%)	43 (48.3%)
1982	263	85 (32.3%)	52 (19.8%)	0 (0%)	126 (47.9%)
1983	362	94 (26.0%)	85 (23.5%)	12 (3.3%)	171 (47.2%)
1984	472	131 (27.8%)	148 (31.4%)	21 (4.4%)	172 (36.4%)
1985	477	106 (22.8%)	175 (36.7%)	17 (3.6%)	179 (37.5%)
Total	1663	431 (25.9%)	491 (29.5%)	50 (3.0%)	691 (41.6%)*

\*  $\chi^2$  for trend=14.2, d.f.=1,  $P<0.01$

logy, with 32 false negatives, giving a predictive value of 84.9% for negative cytology. Thus, a total of 493 malignant and benign masses were correctly identified from a total of 527 masses with adequate cytology and histological diagnoses, giving an overall diagnostic accuracy for aspiration cytology of 93.5%

Cytology was equivocal for 50 aspirates from 48 patients and of these histology was available for 38, of which 36 (95%) were malignant and only 2 (5%) benign.

#### HISTOLOGICAL CATEGORIES

The number of each type of breast mass upon which aspiration cytology had been performed and had been excised is shown in Table V. A significantly higher rate of unsatisfactory aspirates was found in patients with invasive lobular carcinoma compared to those with invasive ductal carcinoma ( $\chi^2=20.71$ , d.f.=1,  $P<0.001$ ). There was a significantly lower rate of unsatisfactory aspirates from patients with fibroadenoma compared with fibroadenosis ( $\chi^2=23.2$ , d.f.=1,  $P<0.001$ ).

#### SIZE OF BREAST LUMP

An analysis of the unsatisfactory rates for different sizes of masses (Table VI) shows that smaller invasive ductal carcinomata ( $\chi^2=17.45$ ,  $P<0.001$ ) and fibroadenomata

TABLE V. Proportion of unsatisfactory aspirates from different histological types of mass

Histology	Total number excised	Number yielding unsatisfactory aspirates
Invasive ductal carcinoma	347	90 (26%)
Invasive lobular carcinoma	33	21 (64%)
Intraductal carcinoma	17	5 (29%)
Other malignant	30	8 (27%)
Total—malignant	427	124 (29%)
Fibroadenosis	160	89 (56%)
Fibroadenoma	94	20 (21%)
Other benign	50	31 (62%)
Total—benign	304	140 (46%)

95% CI\* for difference in unsatisfactory rate between invasive ductal and invasive lobular=20–52%.

95% CI\* for difference in unsatisfactory rate between fibroadenoma and fibroadenosis=21–47%.

\*CI=95% confidence interval.

TABLE VI. Relationship between mass size and the unsatisfactory and false negative aspirate rate

Mass and size	Number excised	Number unsatisfactory	Number false negative
Invasive ductal* carcinoma			
> 3 cm	184	72 (39%)	17 (9%)
< 3 cm	125	13 (10%)	2 (1.6%)
Invasive lobular† carcinoma			
< 3 cm	9	5 (56%)	
> 3 cm	16	9 (56%)	
Fibroadenoma‡			
< 3 cm	59	18 (30.5%)	
> 3 cm	28	2 (7%)	
Fibroadenosis§			
< 3 cm	42	23 (55%)	
> 3 cm	104	60 (58%)	

Sizes not reported: \*38  
†8  
‡7  
§16

( $\chi^2=2.42$ ,  $P=0.07$ ) were associated with a significantly higher unsatisfactory rate than larger tumours. This was not true for invasive lobular carcinoma of fibroadenosis, where the unsatisfactory rate was independent of size. The false negative rate from invasive ductal carcinoma was also significantly higher in smaller tumours.

#### Discussion

Fine needle aspiration cytology of breast masses has been shown to be a simple and safe diagnostic procedure (8–10). This series has confirmed the very high diagnostic accuracy of aspiration cytology, given a satisfactory aspirate (7–10).

The unsatisfactory aspirate rate has improved significantly since aspiration cytology was first introduced in Southampton. This concurs with previous experience (2,6,17). The unsatisfactory rate for the series (41.2%) was high in comparison to the rates in the literature. This may be accounted for by methodological differences: in many centres multiple aspirations are performed to increase the likelihood of a cellular specimen at the patients first consultation (8,10,18). In Southampton, aspiration was only repeated, if necessary, on a subsequent outpatient visit or preoperatively as an inpatient.

A false negative rate of 4% and false positive rate of 0.3% for malignancy from 731 masses excised, compares well with other reports in the literature (2–15,17–20). These figures refer only to the first aspiration results. Repetition of the aspiration would have been expected to reduce the proportion of false negative and positive diagnoses (8,21).

The sensitivity for malignancy of the first aspiration was 64.2% which is relatively low but this is for one aspiration only. Other series have performed multiple aspirations on the same mass but calculate sensitivity as if only one aspiration had been performed. Furthermore, unsatisfactory aspirates have not been included in the calculation of sensitivity for malignancy in other series (3,8,9). This explains quoted sensitivities of up to 95% (22). The extrapolated sensitivity for malignancy, calculated for this series was 91% following three aspiration cytologies. This compares favourably with a sensitivity of 90% on 3 aspirations in Kline *et al.*'s series (9).

This series has confirmed a high accuracy for the technique given a satisfactory aspirate. Our results with a positive predictive value for malignancy of 99.4% and a negative predictive value of 85% were comparable with the results of many studies (7,14,17,22,23). The cardinal principle enunciated by Franzen and Zajicek (24) that a negative aspirate from an otherwise suspicious lump should be regarded as a non-report has been substantiated by this study because only 64% of all the malignant masses gave a positive first cytology.

False positive diagnoses are a reflection of limited experience and not a limitation of the cytological technique (8,9,16). One of the two false positives in this series was diagnosed by an inexperienced cytologist, the other was the result of logistical problems.

The majority of the lesions excised after an equivocal aspirate in this series were histologically malignant. This was a reflection of a strict, conservative approach to diagnostic cytology; a positive diagnosis was only made when there was incontrovertible evidence of malignancy. The grade +1 was used for aspirates considered to be malignant, but well differentiated, of poor cellularity or admixed with benign cells. Many lesions scoring zero on the Southampton scheme would probably be regarded by others as 'suspicious' or 'atypical' and these workers have found a similar high rate of malignancy in suspicious/atypical aspirates (6,9,10,22).

The influence of histology on the unsatisfactory aspirate and false negative rate has been demonstrated in

this study. Forty six per cent of the benign masses but only 29% of the malignant masses produced an unsatisfactory specimen on the first aspiration. This concurs with many series that have found benign masses produce a higher rate of unsatisfactory aspirates (5,8,10,18). In the present series a positive diagnosis was reached in only 29% of the lobular carcinomata compared with 68% of the invasive ductal carcinomata. This compares with figures of 25% and 69% respectively from Eisenburg *et al* (22). Marked fibrosis and hypocellularity have been noted in invasive lobular carcinomata and this may produce difficulty in obtaining representative cellular material (3,24).

In this study, fibroadenoma produced a significantly lower rate of unsatisfactory aspirates than fibroadenosis. This is substantiated by Zajicek's finding that only 20% of aspirates from fibroadenoma had scant epithelial cells whereas 82% of aspirates from fibroadenosis were acellular (8).

Our results concur with previous studies that have shown an association between a high false negative rate for malignancy and small tumour size (3,9,10). Only 2 (6%) of the 32 false negative diagnoses were due to misinterpretation, although a further 4 aspirates did contain atypical possibly malignant cells. Thus for the remaining false negatives it appears that areas of breast tissue adjacent to small tumours were sampled by the aspiration needle.

In conclusion, aspiration cytology is an accurate preoperative diagnostic procedure for the evaluation of breast masses. However unsatisfactory and unrepresentative aspirates result in diagnostic failure in some cases. The incidence of such aspirates is influenced by the histology and size of the mass. An improvement in the unsatisfactory rate would allow more efficient use of resources and better counselling of patients.

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