ORIGINAL ARRTICLE

Fine Needle Aspiration Cytology for Diagnosis of Benign Breast Disease in A Resource-Limited Setting

Aloysius U **OGBUANYA**[1]
Stanley N C **ANYANWU**[2]
Festus. E **IYARE**[3]
Chinedu G **NWIGWE**[1]

[1]*Department of Surgery*
[3]*Department of Pathology*
Alex Ekwueme Federal University
Teaching Hospital, Abakaliki /
Faculty of Health Sciences
Ebonyi State University
Abakaliki, NIGERIA

[2]*Department of Surgery*
Nnamdi Azikiwe University
Teaching Hospital Nnewi/
Faculty of Medicine
Nnamdi Azikiwe University
Awka, NIGERIA

Author for Correspondence
Aloysius U **OGBUANYA**
Department of Surgery
Alex Ekwueme Federal University
Teaching Hospital, Abakaliki/
Faculty of Health Sciences,
Ebonyi State University
Abakaliki, NIGERIA

Phone: +234 803 353 2701
Email: ogbuanyaa92@gmail.com

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ABSTRACT

Background: A majority of breast lesion is benign in nature; benign breast disease is four times more common in Nigerian women. The percentage of unsatisfactory smears in breast cytology appears to be higher in benign conditions compared to malignant ones. The aim of this study is to determine the effectiveness of cytopathology in the diagnosis of benign breast disease in our institution.

Methodology: This is a prospective study of 96 patients with benign breast disease seen during the study period. The patients were subjected to clinical assessment, fine needle aspiration cytology (FNAC) and open biopsy histopathology (as standard reference test).

Results: One hundred and seventy-four patients with both FNAC and histopathology reports were initially evaluated, 96 (55.2%) had benign while the rest (78, 44.8%) harbored malignant lumps. On further analysis of the benign lumps, FNAC achieved high sensitivity (98.8%), specificity (96.9%) and overall diagnostic accuracy (98.0%) compared to clinical assessment with values of 83.3% (sensitivity), 82.1% (specificity) and 82.2% (overall diagnostic accuracy). The false positive rate (FPR, 2.3%) and false negative rate (FNR, 1.6%) reported for FNAC were equally better than figures of 14.9% (FPR) and 20.0% (FNR) documented for clinical assessment. Cytopathology was utilized in sub-classifying 76 (79.2%) out of the 96 biopsy confirmed benign lumps; 49 slides were correctly typed giving a concordant rate of 64.5%.

Conclusion: Fine needle aspiration cytology in our index study showed appreciable concordance with open biopsy histology in the diagnosis and sub-classification of benign breast disease.

***Key words**: Biopsy, Needle, Cytology, Accuracy, Excision*

INTRODUCTION

A vast majority of referred patients with breast diseases presents with breast lumps and receive benign diagnosis when subjected to histopathology examination.[1,2,3,4] Benign breast disease (BBD) has been reported to constitute a heterogeneous group of lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations and neoplasms.[5,6] The term also encompasses a heterogeneous group of lesions that may present a wide range of clinical behaviours, may be detected as incidental microscopic findings and are showing a rising trend worldwide.[5,6,7] McFarlane, working in Jamaica an Afro-Caribbean population examined 333 consecutive breast biopsies and reported a high (80%) incidence of BBD.[8] It was also noted that BBD occurs mainly in young women less than thirty years and the author supports a more conservative approach to diagnosis and management of these patients.[8]

Bearing in mind our unique socio-cultural and economic peculiarities, the ideal initial pre-operative diagnostic tool for breast diseases should be cost-effective, simple with minimal physical and psychological trauma.[9,10,11] Fine needle aspiration cytology (FNAC) of the breast meets these criteria and has become established in many centers all over the world largely due to three reasons; cost containment, advent of image guided biopsies and advancement in cyto-technology including cancer prognostication, grading and sub-classification of breast lesions.[10,12,13]

Selection of patients and clinical conditions most likely to benefit from breast FNAC is essential for high diagnostic yield.[10,12] It has been emphasized that when the components of triple test involving FNAC are in disharmony with each other, even after specialist's review, the use of core needle biopsy to make histopathological diagnosis is warranted.[10,12,14,15]

Earlier studies have shown that both FNAC and core needle biopsy (CNB) of the breast frequently are challenging in differentiating atypical ductal hyperplasia (ADH) from ductal carcinoma-in-situ, diagnosing various papillary lesions and distinguishing benign phyllodes tumours from some fibroadenomas.[10,12,14] This is because CNB may sample non-representative tissue or diseased tissues sampled are not large enough to diagnose the pathology. Again FNAC examines only cellular pattern and background.[10,12] Therefore, excision biopsy is indicated in such conditions when FNAC and CNB fail to make tissue diagnosis, rather than repeating them.[10,14]

From the foregoing, there is need to determine the accuracy of FNAC for benign breast lumps in our setting because of the peculiarities of breast lesions in the African population. Moreover, it has been cited that benign breast disease is four times more common than malignant ones in Nigerian women and that the percentage of unsatisfactory (C1) smears in breast cytology is higher in benign conditions compared to malignant ones.[11,16]

Additionally, many studies have reported preponderance of advanced and extensive breast disease in the black population.[2,4,17] This raises concern over the reliability of FNAC for BBD in our environment because

there is correlation between accuracy of cytological diagnosis and tumour size.[9,18,19,20,21] The aim of this study is to determine the effectiveness of cytopathology in the diagnosis of benign breast disease in our environment.

METHODOLOGY

Design and Setting

This was an eighteen-months prospective study involving all consecutive patients with palpable BBD seen at the breast clinic of Alex Ekwueme Federal University Teaching Hospital Abakaliki, South-East Nigeria from April 2011 to September 2012. The available patients were followed up for five years.

Study Population

In tandem, FNAC and open biopsy procedures were carried out on 174 patients with palpable breast lumps who gave consent and were aged 16 years and above. Furthermore, 96 (55.2%) of these 174 patients had biopsy confirmed benign lumps, FNAC reports and breast ultrasound results and these group formed our study cohorts (patients with benign breast disease). During this study, patients with history of chest or breast irradiation, chemotherapy for breast cancer, mastectomy scars or pregnant women were not included, to minimize errors that may arise as a result of inadequate(C1) or equivocal (C3 and C4) diagnoses.

Procedure

Each of the 174 patients with palpable breast lesions was interviewed and examined at the specialist breast clinic. The relevant clinical details were extracted from the patients and entered into pro-forma. Each patient was examined thoroughly starting with general examination to system-specific examinations with emphasis on the breasts and axillae.

Breast ultrasounds with or without mammography were ordered routinely. Imaging studies were limited to contralateral breasts, axillae and assessment of ipsilateral breasts for architectural details and feasibility of 'Breast Conservation Surgery (BCS)'. Subsequently, FNAC followed by open biopsy was done in all 174 patients, but only those with histopathology – confirmed benign lumps were further evaluated.

Majority of the FNAC test were carried out by the corresponding author. However, those requiring repetitions were performed by the pathologist. During the FNAC test, a 23-gauge disposable hypodermic needle attached to a 10ml plastic syringe was used for the needling of the dominant breast masses. When adequate yield was observed at the needle hub, negatives pressure exerted by the syringe was discontinued, and the aspirate at the needle lumen expelled onto a pre-labeled glass slide using the syringe. The smears were prepared using a second slide inclined at 45 degrees.

Wet fixation of these smears was done by placing the slides on a coplin jar containing 95% ethanol for few minutes. The wet-fixed slides were transported to pathology laboratory for onward staining and reporting by a pathologist. The slides were reported according to the guidelines of National Health Services Breast Screening Program (NHSBSP).[22] The NHSBSP designations include unsatisfactory (C1), benign (C2), atypical (C3), suspicious of malignancy (C4) and unequivocally malignant (C5) categories.

Whenever possible, immediate reporting was adopted, repetition of inadequate smears done and the sub-classification of the lesions attempted. All FNAC results were discussed with the patients and recorded.

The method of open biopsy used was mainly excisional biopsy, but incisional and wedge biopsies were equally done depending on the tumour or patients' characteristics. Majority were done as day cases using 0.5% xylocaine for local infiltrative anaesthesia. The remaining patients were biopsied either under general anaesthesia or local anaesthesia augmented with sedation. Breast incisions were placed on the consideration of oncoplastic implications. Combined instrument and diathermy dissections enhanced haemostasis and specimen retrieval. Drains were used but not routinely.

All resection specimens were placed in labeled containers containing 10% formal saline for preservation. The specimens were transported to histopathology laboratory accompanied by properly completed histology request form. A single pathologist reported all the slides. The pathologist was blinded from the true identities of the patients during the stages of the FNAC and open biopsy. Follow up visits were arranged with the patients to discuss the final diagnoses and take informed decision. Only the 96 patients with biopsy-proved benign lesions were further evaluated.

Statistical Data Analysis

This was done using statistical package for social sciences (SPSS), software version 22.0 (IBM, USA 2015). The FNAC validities for benign breast disease were calculated using the standard statistical formulae.[23] Descriptive statistics were employed to calculate categorical variables like percentages. The results were presented in tables. Mean and standard deviation were used to summarize continuous variables. Where appropriate, Chi-square test was used to test for the level of significance of the variables. Confidence interval was calculated at 95% level and significance at 5% probability level (P<0.05).

Ethical Approval

The proposal for the study was approved by the research and ethics committee of Alex Ekwueme Federal University Teaching Hospital Abakaliki, South-East Nigeria before commencement of the study. All ethical principles relating to studies involving human subjects were observed throughout the period of the study. All the patients that participated in this study gave informed written consent before commencement of the study.

RESULTS

A total of 210 patients with breast complaints were seen in the breast clinic during the study period, but 11 of them declined FNAC test giving an FNAC default rate of 5.2%. The cost of FNAC test in our centre was one thousand five hundred naira (approximately four US dollars). The rest (199, 94.8%) gave consent for and did FNAC, but ultimately, only 174 (87.4%) accepted open biopsy, giving an open biopsy default rate of 12.6%.

Histology confirmed 96 (55.2%) benign and 78 (44.8%) malignant cases, but clinical examination quoted 94 (54.0%) benign and 80 (46.0%) malignant diagnosis. Of the 94 benign diagnoses by clinical assessment, histology confirmed 80 to be truly benign and the

remaining 14 malignant. Similarly, out of the 80 malignant diagnoses from clinical examination, histology confirmed that 64 were malignant and 16 benign (Table 1). The 96 patients with biopsy confirmed benign breast lumps formed our study cohorts and were further evaluated.

Table 1. Correlation of Clinical and histologic diagnosis

Clinical Examination		**Histopathology Report**	
Clinical Diagnosis	**Freq**	**Benign**	**Malignant**
Benign	94	80	14
Malignant	80	16	64
Total	174	96	78

The age range of the 96 patients with benign breast disease was 16-75years with a mean of 32.9±SD 15.8 (Table 2).

Table 2. Age distribution of the patients with benign breast disease

Age range	**Freq**	**Percentage**
10 – 19	18	18.7
20 – 29	31	32.3
30 – 39	22	22.9
40 – 49	10	10.4
50 – 59	07	7.3
60 – 69	4	4.2
70 – 79	4	4.2
Total	**96**	**100.00**

Histology findings indicate that majority (10, 71.4%) of 14 patients with equivocal (C3 and C4) smears from FNAC reports have malignant disease. On the other hand, nearly two-third (seven, 63.6%) of 11 patients with unsatisfactory (C1) cytological diagnosis received benign diagnosis following histopathology (Table 3). The results of diagnostic validities of FNAC and clinical examination for benign breast diseases, using open biopsy histopathology as reference standard is shown below (Table 4).

Table 3. Frequency distribution of cytological and histology correlation

Cytology	**Freq**	**Benign**	**Malignant**
C1	11	07	04
C2	86	84	02
C3	06	02	04
C4	08	02	06
C5	63	01	62
Total	**174**	**96**	**78**

C1=inadequate/unsatisfactory; C2=Benign; C3=atypical; C4=suspicious; C5=unequivocally malignant

Histology also revealed that over four-fifth (85.4%) of the benign lesions were contributed by fibro-epithelial breast lesions (fibroadenoma, fibrocystic change and phyllodes tumour) and less than 10.0% by minor breast tumours (Table 5).

The median age was 19.82 years. Benign breast disease of male represents 1.0%(1 patient) of patients with BBD and 0.6% of patients with breast lumps during the period under review.

Table 4. Validity results of FNAC and clinical diagnosis for benign breast disease

Validity of BBD(%)	**Sensitivity**	**Specificity**	**FPR**	**FNR**	**PPV**	**NPV**	**ODA**
FNAC Test	98.8	96.9	2.3	1.6	97.7	98.4	98.0
Clinical diagnosis	83.3	83.1	14.9	20.0	85.1	80.0	82.8

FNAC= Fine needle aspiration cytology; FPR=false positive rate; FNR=false negative rate; PPV=positive predictive value; NPV=negative predictive value; ODA=overall diagnostic accuracy. BBD= benign breast disease.

Table 5. Frequency distribution of histo-pathological diagnosis

Histopatholgic diagnosis	Freq	%
Fibroadenoma	57	59.4
Fibrocystic change	23	24.0
Duct ectasia	4	4.3
Lactating adenoma	2	2.1
Sclerosing adenosis	1	1.0
Granula cell tumour	1	1.0
Gynaecomastia	1	1.0
Lipoma	1	1.0
Galactocoele	1	1.0
Fat necrosis	1	1.0
Chronic mastitis	2	2.1
Benign phyllodes tumour	2	2.1
Total	**96**	**100.0**

There were no patients with dual pathology on one or both breasts, though 12 (12.5%) of the 96 patients with BBD had bilateral disease and another eight (8.3%) of these patients with BBD harbored multiple lumps either on the left or right side.

The results of FNAC sub-classification of biopsy-confirmed benign lesions are shown below (Table 6).

Out of 42 fibroadenomas sub-classified by FNAC, histology showed that 29 were truly fibroadenomas while 13 were proved to be other pathologic entities namely: six fibrocystic change, three duct ectasia and one each of phyllodes tumor, lactating adenoma, sclerosing adenosis and gynaecomastia. Of the 25 fibrocystic change sub-classified, 16 were confirmed by histology to be truly so while the remaining nine turned to be seven fibroadenomas and one each of benign phyllodes and lactating adenoma after histology. Among the 20 (20.8%) unclassified smears, histopathology revealed that 14 were fibroadenomas and one each of fibrocystic change, gralactocoele, granular cell tumour, mastitis, fat necrosis and lipoma.

Of the three duct ectasia identified by FNAC, one was confirmed so while the remaining two were proved by histology to be fibroadenomas. Similarly, of the two mastitis typed by FNAC, histology showed one to be mastitis and the other, fibroadenoma. The four FNAC smears designated as benign phyllodes were all found to be fibroadenomas after histopathology of the entire resection specimen.

When unsatisfactory (C1) smears were assumed benign and equivocal (C3 and C4)

Table 6. Frequency distribution of cytological sub-classification of BBD by FNAC

FNAC sub-classification	Frequency	Histopathology		Concordance (%)
		True	False	
Fibroadenoma	42	29	13	69.0
Fibrocystic change	25	16	9	64.0
Duct Ectasia	3	1	2	33.3
Chronic Mastitis	2	1	1	50.0
Benign Phyllodes	4	2	2	50.0
Unclassified	20	-	-	-
Total	**96**	**49**	**27**	**64.5**

FNAC= Fine needle aspiration cytology; BBD=Benign breast disease.

smears assumed positive for malignancy, FNAC showed that 79 out of 98 lumps that felt "firm" during needling were benign while 19 were malignant. Histopathology confirmed that all the 79 benign cytological diagnosis were truly benign while 12 of the 19 malignant cytological diagnoses were malignant and seven truly benign. Conversely, only six of the 53 lumps that felt 'hard or gritty' during aspiration received benign cytological diagnosis while 47 (88.7%) were typed malignant. Histology confirmed all 47 slides to be truly malignant, but of the 6 benign FNAC results, histology held that 3 each were malignant and benign, respectively.

Eleven of the 23 lumps that felt 'soft' during needling were designated benign via cytology, but histology confirmed that seven of these were benign and four malignant. All 12 'soft' lumps that received malignant cytological diagnosis were confirmed malignant by histopathology.

With respect to benign breast lumps, the sensitivity, specificity, overall diagnostic accuracy and false positive rate recorded by FNAC for tumors that felt 'firm' during needling were 91.9%, 100.0%, 92.9% and 0.0% respectively. For tumors that felt 'hard' during aspiration, sensitivity, specificity, diagnostic accuracy, FPR and FNR were 100.0%, 94.0%, 94.4%, 33.3% and 0.0% respectively. For 'soft' tumors, sensitively, specificity, overall diagnostic accuracy and FNR were 100.0%, 70.6%, 78.3% and 0.0% respectively. When inadequate (C1) and equivocal (C3 and C4) smears were excluded, FNAC was unequivocally benign in 86 (89.6%) of the 96 patients with biopsy-confirmed benign breast disease compared to a concordance of 85.1% for clinical assessment alone.

DISCUSSION

Fine needle aspiration cytology was accepted by majority of the patients that attended breast clinic; only 5.2% of them defaulted from the test compared with 12.6% default rate for open biopsy. The enthusiastic acceptance of FNAC has been attributed to its simplicity (an office procedure without need for anaesthesia), price containment, minimal invasiveness, rapid diagnosis and low complication rates.[10,12,14,15]

Fibroadenoma was the predominant histological diagnosis with over half (59.4%) of the entire patients with benign lumps harboring fibroadenomas followed by fibrocystic change (24.0%) and duct ectasia (4.3%). These findings conform with reports from Africa and Asia, but in the UK and USA, fibrocystic disease was more frequent than fibroadenoma.[1,2,3,4,6,7] The reasons for these differences were related to genetic and environmental variations.[7]

FNAC performed better than clinical assessment in this study for a number of reasons. First, the adoption of immediate slide repetition for inadequate smears offers opportunity for a 'second look' in the breast cytopathology; this was not applicable to clinical diagnosis. Studies have shown that the diagnostic yield is increased by examining the aspirates immediately and repeating the procedure if the samples obtained were unsatisfactory.[10,12,16,24]

Second, the phenomenon of tactile sensation as a clinical index of fingertip sensitivity allowed FNAC to utilize both clinical and cytological criteria to achieve a synergistically

informed decision for an augmented and accelerated diagnosis.[10,12] Robert and Rainsbury emphasized that this clinical sign could enhance the accuracy of FNAC by suggesting the possibility of a benign or malignant diagnosis during needling.[9,10,14,25] A malignant diagnosis was given if a gritty sensation is felt while if a rubbery, firm sensation is felt, a benign diagnosis was entertained.[9,10] Indeed, all 79 out of 98 breast masses that felt firm and rubbery during needling received benign cytological diagnosis and these 79 lumps were subsequently confirmed benign by histology. Reports culled from Jos and Lagos, both in Nigeria support the above findings.[9,25]

Third, there are known FNAC pitfalls and patients can be selected properly from outset. It has been cited that FNAC perform poorly for pregnancy related lesions and in certain breast lesions like lipoma, sclerosed fibroadenomas, fibrous mastopathy, hypertrophic scar, low grade tumours, or tumors previously subjected to neoadjuvant chemotherapy or radiotherapy because they are inherently acellular or hypocellular.[10,12,14] Insight on the nature of these tumours may be obtained through prior clinical and/or radiological evaluation and this should necessitate selection of open biopsy as the first option for pathologic assessment of these tumors rather than FNAC.[10,12]

The diagnostic validities of FNAC for benign lumps in this study showed impressive results. An overall diagnostic accuracy of 98.0% is comparable to figures from Lagos (Nigeria), Australia, Bethesda (USA), United Kingdom and Hong Kong.[9,10,12,13,19] The sources of error in the FNAC validity test for benign breast disease in this study include two missed benign (C2) diagnoses wrongly reported as malignancies, one truly benign lump typed as malignant cytology, four truly benign lumps masquerading as equivocal (C3 and C4) smears and seven histology-proved benign lumps designated unsatisfactory (C1) smears by cytopathology(Table 4).

The preponderance of benign disease among unsatisfactory smears has been attributed to difficulty in dislodging cells from a subset of benign lesions that are inherently fibrotic.[10,11,19] The seven benign lumps that were categorized unsatisfactory were found to comprise of three fibroadenomas, two fibrocystic change and one each of duct ectasia and mastitis by histopathology. Overall, unsatisfactory smears contribute to diminished accuracy of FNAC for benign lumps.

The false positive rate (FPR) of 2.3% recorded for BBD in this study was contributed by one low grade invasive ductal carcinoma and one mucinous carcinoma, both mimicking benign cytology. It has been shown that malignant cells may be too scanty, obscured by artifact or show atypical features more marked than in C3 and C4 categories, but not diagnostic of malignancy.[10,12,25] Similarly, the cause of a false negative diagnosis in the index study was due to a fibroadenoma incorrectly reported as unequivocally malignant (C5) smear due to its atypical cytological pattern.

This incorrect cytological diagnosis may be due to one or more of the following. First, fibroadenomas are by definition fibroepithelial, biphasic neoplasms that exhibit a wide range of clinical behaviors.[5,10] Cellular or hyperplastic fibroadenomas, complex

fibroadenomas and fibroadenomas with atypical foci are common reasons for false positive cytological diagnoses.[10,19,21,26] Second, fibroadenomas are very mobile and perhaps, this may affect stabilization and fine needle localization especially for lumps less than 2.0cm[10,16,1921,26]. Third, fibroadenomas share overlapping cyto-morphological features with breast diseases like papillary lesions and phyllodes tumours.[10,19]

The utilization of FNAC in this study moved beyond simple FNAC diagnosis to definitive cytological diagnoses using specific cyto-morphological criteria. Of the 76 BBD sub-classified, histopathology confirmed 58 to be truly so, giving a concordance of 76.3%. The eight slides that were wrongly typed in the case of fibroadenomas were probably due to lack of full cytological features to define fibroadenomas. Generally, it has been cited that materials retrieved during needling can be used for sub-classification and evaluation of multiple biologic indicators like hormone receptor status, grading and other prognostic and predictive indices of breast cancer.[10,12,13,27]

CONCLUSION

Fine needle aspiration cytology in this study represents a useful technique in the preoperative diagnosis and sub-classification of benign breast disease in a resource-limited setting like ours. Overall, FNAC is a cheap, simple, reproducible, minimally invasive diagnostic test. It is important to emphasize that FNAC is not a substitute for open or core needle biopsies, rather, with judicious selection, it should be used to complement histopathological test in the triple assessment of patients with dominant breast masses.

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