Original Article

Eur J Breast Health 2017; 13: 194-9
DOI: 10.5152/ejbh.2017.3506

Sub-classification of Breast Masses by Fine Needle Aspiration Cytology

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ABSTRACT

Objective: The aim of this study is to evaluate the accuracy of sub-classification of breast diseases using Fine Needle Aspiration cytology (FNAC).

Materials and methods: A one-year prospective study of 180 consecutive patients with palpable breast lesions who underwent FNAC and subsequently open surgical biopsy for histological confirmation. FNAC was used to sub-classify breast lesions and then correlated with histological diagnosis.

Results: A total of 180 patients were enrolled into the study but only 110 patients with histology report were used for test validity. Seventeen (15.5%) smears were C1; while 46 (41.8%), 5 (4.5%), 4 (3.6%) and 38 (34.6%) were C2, C3, C4 and C5, respectively. FNAC achieved sensitivity of 90.0%, specificity of 95.5%, false positive rate of 5.3%, false negative rate of 8.7%, positive predictive value of 94.7%, negative predictive value of 91.3% and overall diagnostic accuracy of 92.9%. Only 86 (78.2%) of the 110 smears could be sub-classified into different disease conditions of the breast on cytology. FNAC accurately sub-classified 25(78.1%) of fibroadenoma and 28(87.5%) of invasive ductal carcinoma.

Conclusion: FNAC can reasonably sub-classify fibroadenoma, invasive ductal carcinoma and mastitis but there is still a challenge with lobular carcinomas, metaplastic carcinomas, papillary carcinomas and fibrocystic changes.

Keywords: Cytology, breast masses, sub-classification.

Cite this article as: Madubogwu CI, Ukah CO, Anyanwu SNC, Chianakwana GU, Onyiaorah IV, Anyiam DCD. Sub-classification of Breast Masses by Fine Needle Aspiration Cytology. Eur J Breast Health 2017; 13: 194-199.

Introduction

Breast lump is one of the commonest presentations of breast diseases. The diagnosis of breast diseases can be achieved like in other clinical conditions using: history, physical examination and investigation which include cytological or histological confirmation. Currently, several studies have advocated the use of 'Triple test' which consists of clinical examination, radiologic examination and cytopathology as more accurate means of making diagnosis of breast lesions (1-5). When all the three components are positive, diagnostic accuracy approaches 100% for malignancy (2). Fine Needle Aspiration cytology (FNAC) is widely used and accepted as a reliable method of making initial pre-operative diagnosis in breast diseases (2, 6). It has been credited with a lot of advantages such as: high accuracy, cheap, fast, out-patient procedure reducing pressure on theatre load, high patient acceptability, and low complication rate (2, 6).

Fine Needle Aspiration cytology reports are classified into 5 categories based on the National Health Services Breast Screening Programme (NHSBSP) of Britain (7). The use of these standardized diagnostic categories is necessary to enhance communication within a multi-disciplinary team and for comparing results from other Centres. The diagnostic categories and their corresponding numerical codes are: Inadequate/insufficient (C1); Benign (C2); Atypical/indeterminate (C3); Suspicious of malignancy (C4) and Malignant (C5). However, Specimen from FNAC can be used to sub-classify breast lesions (7-9). Most studies on FNAC do not make attempt at sub-classifying breast lesions into definite disease types because of the challenges usually encountered (8, 9). The aim of this study is to evaluate the accuracy of sub-classification of breast diseases using FNAC in our Centre.

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Received: 16.03.2017
Accepted: 18.06.2017

Materials and Methods

This is a one-year prospective study of all the consecutive patients with palpable breast lesion presenting at the two general surgery out-patient clinics of the University Teaching Hospital. Approval was sought from the Ethical committee of the University Teaching Hospital before the commencement of the study. The procedure was duly explained to the patients, and that the lump will be removed for histology after the FNAC. Their informed written consent was obtained. Patients who had FNAC were followed up until the histology report was obtained following open surgical biopsy.

Patient lies supine on a couch after exposure of the upper half of the body. The surgeon after washing hands with soap and water wears a pair of surgical gloves. The skin of the breast over the lump was disinfected using gauze soaked in 75% methylated spirit. The dominant hand was used to handle the syringe with 25G needle in place. The other hand was used to stabilize the tumour within the breast. The needle on the syringe was then advanced into the tumour and negative pressure was generated by pulling on the plunger and maintaining the pressure with the fingers and thumb. The needle was moved in and out in different directions in the tumour while maintaining the negative pressure. The movement of the needle continues until adequate material appears in the hub of the needle. The negative pressure was released and the needle withdrawn from the breast. The syringe was separated from the needle, filled with air, re-attached to the needle and its content expressed onto the centre of the microscope slides (wet and dry). Smears were made by spreading the aspirate using another clean slide placed at 45 degree and running it over the slide. The wet slide was fixed by putting it into a Coplin jar containing 95% ethanol while the dry slide was fixed by air-drying (for at least 5 minutes). The two groups of slides were then transported to the laboratory for staining and cytology reporting. If material aspirated was insufficient, further needle passes were done. If the lump is cystic, the entire cyst was completely aspirated, labelled and sent to laboratory for centrifuging and further processing. Residual masses after cyst aspiration were handled like other solid masses.

The wet slides were stained with Papanicolaou staining technique while the dry slides were stained using May-Grunwald-Giemsa staining technique. The patients were also worked up for open surgical biopsies and the samples collected from each patient was immersed in a container with 10% formalin and transported to the histopathology laboratory for preparation and reading.

The cytology and histology reports were documented in the pro-forma used for the study when they were ready. The cytological diagnoses were categorized into one of the five diagnostic categories according to the recommendations of the United Kingdom National Health Services Breast Screening Programme (NHSBSP) (7). The breast samples from FNAC were further sub-classified into definite breast disease entities. The final histopathological diagnosis of each case was then compared with the cytological diagnosis.

The data were entered into a database and statistical analyses carried out using the Statistical Package for Social Sciences (SPSS) version 17.0. (SPSS Inc. Released in 2008; SPSS Statistics for Windows, Version 17.0. Chicago, USA). The results were presented in frequency tables and cross tabulations.

Results

A total of 180 patients were enrolled into the study. All had clinical evaluation as well as FNAC. Only 113 patients had open biopsy with Histology report. Sixty-seven patients defaulted from open surgical biopsy due to one reason or another. The above finding gives a biopsy rate of 63% and default rate of 37%. Only patients who had open biopsy with histology reports were further evaluated. Out of the 113 patients with histology report, two showed normal breast tissues and another one, inadequate specimen. Of the two cases of normal histology, one was C4 and the other C1 on FNAC while the case with inadequate specimen on histology was C5 on FNAC. The three were further excluded leaving only 110 patients who were used in the comparative aspect of the study, and to test validity.

Thirty-eight (34.6%) smears were unequivocally malignant (C5) while 46 (41.8%) were benign (C2) i.e. negative for malignant cells. Five (4.5%) smears were probably benign (C3) while 4 (3.6%) smears were suspicious for malignancy (C4). Seventeen (15.5%) smears were unsatisfactory/inadequate (C1) giving an unsatisfactory rate of 15.5%.

Out of the 38 cases that were positive for malignancy on cytology, 36 of them were true positive and two were false positive. Out of 46 cases that were benign on cytology, 42 were true negative while four were false negative. Out of the 17 unsatisfactory cases on cytology, nine were benign on histology while eight were malignant. Three out of the five cases that were probably benign on cytology were confirmed benign on histology while two were confirmed malignant. Out of the four cases suspicious for malignancy on cytology, two were benign on histology while two were confirmed malignant (Table1).

Diagnostic validities of FNAC when both unsatisfactory and suspicious smears are excluded is shown in Table 2.

Table 1: Cytology report/ Histology type

		Histology type		
		Benign	**Malignant**	**Total**
Cytology	Unsatisfactory(C1)	9	8	17
report	Benign(C2)	42	4	46
	Probably benign(C3)	3	2	5
	Probably malignant(C4)	2	2	4
	Malignant(C5)	2	36	38
Total		58	52	110

Table 2: Diagnostic validities of FNAC excluding unsatisfactory and suspicious smears

Diagnostic validity	**Value in percentage**
Sensitivity	90.0
Specificity	95.5
False positive rate	5.3
False negative rate	8.7
Positive predictive value	94.7
Negative predictive value	91.3
Overall diagnostic accuracy	92.9

FNAC: Fine Needle Aspiration cytology

Table 3: Sub-classification of cytology results

Frequency	Percent	
Fibroadenoma	32	29.1
Invasive lobular ca	1	.9
Invasive ductal ca	32	29.1
Mastitis	2	1.8
Fibrocystic change	8	7.3
Fat necrosis	3	2.7
Benign proliferative lesion	2	1.8
Benign cystic lesion	2	1.8
Metaplastic ca	3	2.7
Papillary ca	1	.9
Unclassified	24	21.8
Total	110	100.0

Only 86 (78.2%) of the 110 smears could be sub-classified into different disease conditions of the breast on cytology. Twenty-four (21.8%) smears could not be sub-classified. Out of the 86 smears sub-classified, fibroadenoma was 32 in number and invasive ductal carcinoma was also 32 in number. The rest of the sub-classes are shown below (Table 3).

Out of the 32 diagnosis of fibroadenoma on FNAC, histology confirmed: 25 (78.1%) to be fibroadenoma, five (15.6%) to be fibrocystic changes and one (3.1%) each of invasive ductal carcinoma and mastitis. Also, out of another 32 diagnosis of invasive ductal carcinoma by FNAC, histology confirmed: 28 (87.5%) of them to be invasive ductal carcinoma and the remaining 4 (12.5%) to be metaplastic carcinoma.

Discussion

Fine needle aspiration cytology (FNAC) was found to be more specific than sensitive in this study, 95.5% and 90.0%, respectively with overall diagnostic accuracy of 92.9% (Table 2). These values are comparable to those documented in similar studies (10-14) and much higher than >60% for specificity and > 80% for sensitivity recommended by NHSBSP of Britain (7). The high values for sensitivity, specificity and overall diagnostic accuracy obtained in this study may be due to the fact that only palpable lumps were sampled and the fact that most of the patients presented late with large lumps. With sensitivity of 90.0% in this study, it means that the diagnosis of malignancy can be made about 90% of the times by FNAC. Also with specificity of 95.5% obtained in this study, it means that FNAC can exclude malignancy in about 95.5% of the cases. And with overall diagnostic accuracy of 92.9%, it shows that FNAC can make diagnosis of both benign and malignant diseases in about 92.9% of the cases.

Apart from telling whether a lesion is benign or malignant, FNAC can significantly sub-classify breast lesions into definite histological entities. According to the study by Young et al (8), FNAC of the breast is a reliable method for the diagnosis of breast carcinoma but difficulties still exist in their ability to determine tumour sub-type. In the above study, performance was best for the diagnosis of adenocarcinoma (ductal type) with 65% accuracy. The rates for exact diagnosis of lobular, medullary and mucinous carcinomas were 20%, 12%, and 27%, respectively.

In the current study, only 86 (78.2%) of the 110 smears could be sub-classified into different histological conditions of the breast on cytology. Twenty-four (21.8%) smears could not be sub-classified. Out of the 86 smears sub-classified by FNAC, fibroadenoma was 32 in number and invasive ductal carcinoma was also 32 in number. Correlation of FNAC sub-classification with histopathology results showed that: out of the 32 diagnoses of fibroadenoma on FNAC, histology confirmed: 25 to be fibroadenoma giving an accuracy of 78.1%, five to be fibrocystic changes and one each of invasive ductal carcinoma and mastitis. Also, out of another 32 diagnoses of invasive ductal carcinoma by FNAC, histopathology confirmed: 28 of them to be invasive ductal carcinoma with an accuracy of 87.5% and the remaining four to be metaplastic carcinoma. Three diagnoses of metaplastic carcinoma on FNAC proved to be two invasive ductal carcinomas and one metaplastic carcinoma on histopathology. Also, a diagnosis of papillary carcinoma on FNAC was confirmed invasive ductal carcinoma on histopathology. One diagnosis of lobular carcinoma on FNAC proved to be mastitis on histopathology. Two cases of mastitis on FNAC were accurately diagnosed as mastitis on histopathology. Also, out of the eight cases of fibrocystic changes by FNAC, four were fibrocystic changes while three were invasive ductal carcinoma and one adenosis on histopathology (Table 3).

The accuracy of FNAC in this study to sub-classify breast diseases was comparable to that by Young et al (8) in their study on diagnosis and sub-classification of breast carcinoma by FNAC. The current study however achieved higher accuracy of 87.5% compared to 65% by Young et al (8) for invasive ductal carcinoma. However, making accurate diagnosis of metaplastic carcinoma, papillary carcinoma, lobular carcinoma and fibrocystic changes is still a problem. Maygarden et al (9) in their study on sub-classification of benign breast disease by fine needle aspiration cytology, comparing cytological and histopathological findings in 265 palpable breast masses found that overall, the specific diagnosis was correct in 80% of cases. This is comparable to the accuracy of 78.1% for fibroadenoma obtained in the current study. Also, in another study by López-Ferrer et al (15) on Fine needle aspiration cytology of breast fibroadenoma, correlating the cytopathology and histopathology of 405 cases, cytohistological agreement was present in 287 of the 362 cytodiagnoses. This ensured the sensitivity of the cytological diagnosis of Fibroadenoma to be 86.9% with a positive predictive value of 79.3%. This is slightly higher than the value obtained in this present study.

Only 113 of 180 patients initially recruited for the study presented for open surgical biopsy and histopathology. Sixty-seven patients defaulted for some reasons and that formed a major limitation for the study.

Conclusion

Fine needle aspiration cytology can reasonably sub-classify fibroadenoma, invasive ductal carcinoma and mastitis but there is still a challenge with lobular carcinoma, metaplastic carcinoma, papillary carcinoma and fibrocystic changes.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University Teaching Hospital.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Design - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Supervision - C.I.M., C.O.U., S.N.C.A., G.U.C.; Resources - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Materials - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Data Collection and/or Processing - C.I.M.; Analysis and/or Interpretation - C.I.M.; Literature Search C.I.M.; Writing Manuscript - C.I.M., C.O.U.; Critical Review - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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APPENDIX

APPENDIX A: Diagnostic category:

1. Inadequate/insufficient (C1): This category is used when the smears are too sparsely cellular or distorted to allow a microscopic diagnosis or the aspirate is inconsistent with the clinical and image findings. Since this is a subjective diagnosis an explanation of why the sample is inadequate/insufficient should be given.
2. Benign (C2): This diagnostic category is used when the sample is adequate and shows no evidence of malignancy.
3. Atypical/indeterminate (C3): This category is used when smears with benign features also show features which may be seen with malignancy, such as loss of cohesion or nuclear atypia. Another possible circumstance includes a lesion in which the cellularity is low with subtle cytological atypia. Aspirate showing papillary features or having mucin may also be placed in this category, depending on the circumstances.
4. Suspicious of malignancy (C4): This diagnostic category is used when the smears show features suggestive of but not diagnostic of malignancy. The malignant cells may be too scanty, obscured by artefact or show atypical features more marked than in the atypical or indeterminate category but not diagnostic of malignancy.
5. Malignant (C5): This diagnostic category is used when the aspirate is clearly malignant. This diagnostic category includes invasive breast carcinoma, ductal carcinoma in-situ and other malignancies.

APPENDIX B: Conditions associated with false positive diagnosis in FNAC:

False positive diagnosis in FNAC is frequently due to difficulties with interpretation. Some of the conditions associated with false positive diagnosis include:

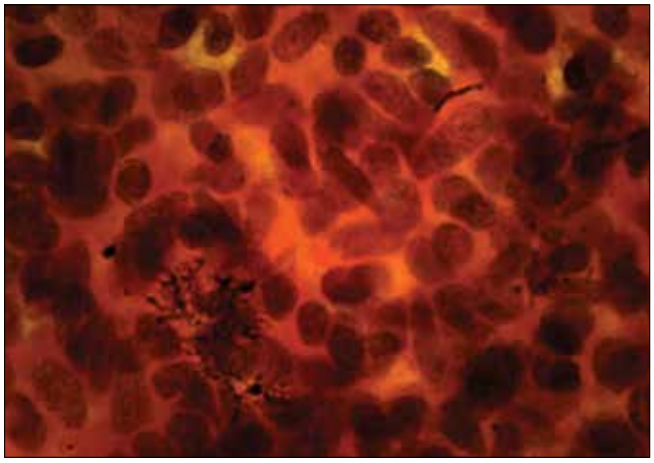
1. Fibroadenoma with atypical features.
2. Mass or thickening associated with lactation.
3. Radial scar with hyperplasia.
4. Papilloma: It is usually impossible to reliably differentiate between papilloma, atypical papilloma, intra-cystic papillary carcinoma and invasive papillary carcinoma based on cytology material alone.
5. Radiation changes: Radiation induced epithelial atypia is common in benign breast tissue after treatment. Similar problem may arise following chemotherapy.
6. Fat necrosis: Triple test here may be misleading as fat necrosis can mimic carcinoma both clinically and on imaging.
7. Atypical apocrine cells: Differentiating apocrine metaplasia and apocrine carcinoma can occasionally be difficult.
8. Gynaecomastia.
9. Phyllodes tumour.
10. Adenomyoepithelioma.
11. Tubular adenoma.
12. Granular cell tumour.

APPENDIX C: False negative diagnosis in FNAC:

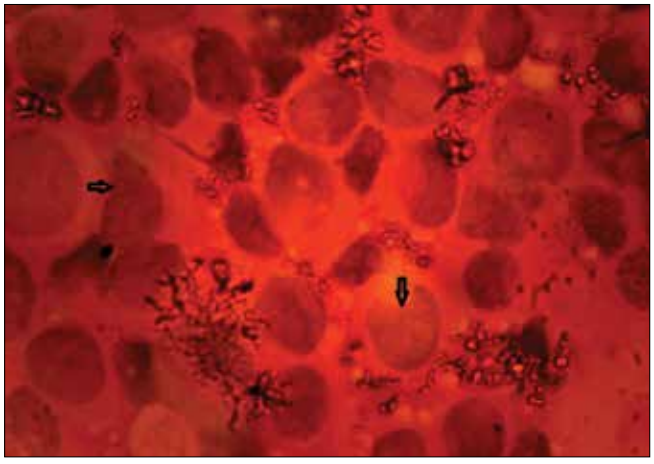
False negative diagnoses are most commonly as a result of sampling error and at times due to interpretation error. Some of the situations and conditions associated with false negative diagnoses in FNAC include:

1. Difficulty in sampling some lesions, for example: small malignant lesions that are well differentiated and sclerotic, masses that are difficult to feel and lesions close to the chest wall.
2. Well differentiated grade I cancer, as cell yield may be poor or only have mild cellular atypia.
3. Infarcted papilloma.
4. Invasive lobular carcinoma may yield only few cells.
5. Low grade ductal carcinoma in-situ, some tubular carcinoma and cribriform carcinoma my yield deceptively 'benign' aspirates.
6. Inflammatory carcinomas, no definite mass may be palpable.
7. Necrosis in the centre of a high grade carcinoma.
8. Sclerosis which is a potential cause of a low cell yield.
9. Papillary carcinomas which requires excision and examination of the whole lesion and capsule.
10. Mucinous tumours are often well differentiated and the cell yield may be poor.

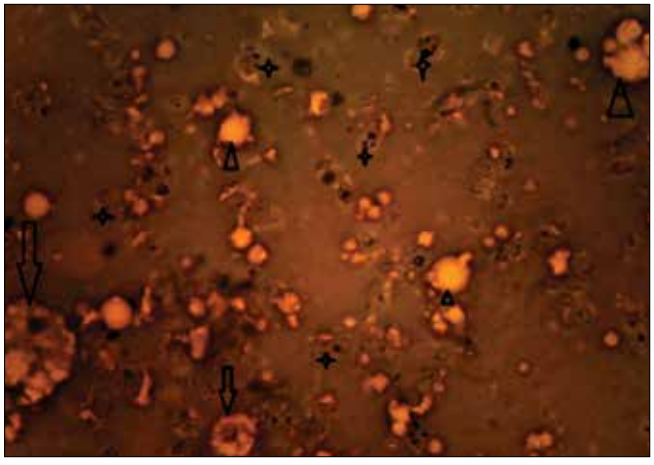
APPENDIX D: Photomicrograph of common breast diseases:



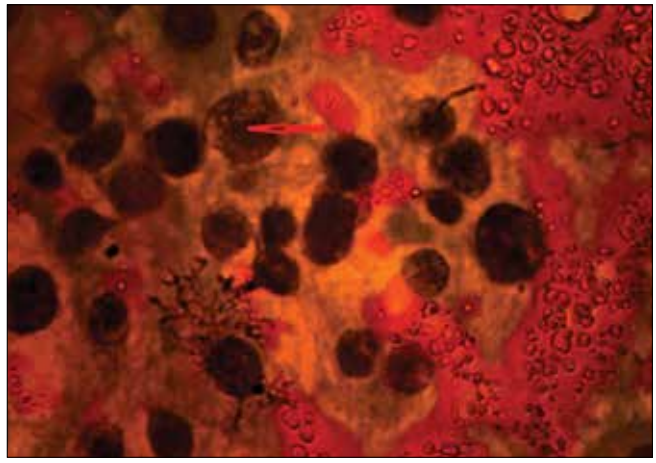
Photomicrograph of fibroadenoma {x1000 magnification; Papanicoloua Stain}:-. At this magnification ductal cells with bland nuclear features admixed with myoepithelial cells can be appreciated.



Photomicrograph of metaplastic carcinoma of breast (x1000 magnification; Papanicoloua Stain):- At this magnification highly pleomorphic nuclei with irregular nuclear margins are depicted by the two arrows can be appreciated.



Photomicrograph of fibrocystic changes {x400 magnification; giemsa stain):- In the background are many foamy macrophages, fat droplets and neutrophil polymorphs as depicted by arrows, arrowheads and stars, respectively.



Photomicrograph of invasive ductal carcinoma, not otherwise specified {x400 magnification; Papanicoloua Stain}:-At this magnification the loose cluster of tumour cells is seen to be composed of neoplastic ductal cells with pleomorphic hyperchromatic nuclei and abundant granular cytoplasm. Some of the cells contain prominent nucleoli as depicted by the arrow.