

Original Research Article

An Audit Of Fine Needle Aspiration Cytology Diagnosis Of Breast Lesions in Calabar, Nigeria.

ABSTRACT

AIM: The aim of this study is to determine the reliability of fine needle aspiration cytology (FNAC) of the breast as rapid cheap and quick diagnostic tool in an underdeveloped setting.

Study Design: A descriptive retrospective study of breast FNAC results matched with the open biopsy results of 93 breast lesions between January 2012 to October 2014.

Place and duration of study: University of Calabar teaching hospital, January 2012 to October 2014.

Methodology: Data and archival slides of FNAC and their matched histological slides were analysed. The FNAC diagnosis were compared with the histological diagnosis, which are assumed to be the gold standard. The FNAC concordance with histological diagnosis was tested for quality by comparing our results to the United Kingdom's NHS breast cancer screening programme (NHSBSP) standard of quality.

Result: Ninety three patients (93) had FNAC of the breast followed by open biopsy with histology; comprising one male 92 females giving a male female ratio of 1:0.01. The complete sensitivity 90.7%, absolute sensitivity 72.1% (95% CI: 55.3-84.7%), and full sensitivity, 88.1% (95% CI: 74.4 - 96.0%) of our test, met the performance target of NHSBSP guidelines. However, the false negative rate and the false positive rate of our test results did not meet the NHSBSP performance target.

Conclusion:

Fine needle aspiration cytology diagnosis of the breast offers a cheap and quick means of diagnosis, however more needs to be done to improve its diagnostic reliability and safety in Calabar.

Keywords: *Calabar, Fine needle aspiration, Audit,, NHSBSP*

1 INTRODUCTION:

Fine needle aspiration cytology (FNAC) was introduced as a rapid and cheap diagnostic tool of palpable breast masses in the University of Calabar teaching hospital (UCTH), nearly four decades ago. From the time of the pioneer practitioners - Prof Ed B Attah (Pathology) and Okuku Prof A.A. Otu (Surgery), its

effectiveness has not been subject to audit, even though a third generation of practitioners is now in place. It is now accepted that FNAC should be employed as part of a triple approach to diagnosis, which involves breast clinical examination, mammography for women 35 years and above and or core needle biopsies so as to improve its sensitivity(1-4).Among its many uses, are to diagnose malignant breast diseases so as to plan definitive surgeries, at the same time those with benign diseases, reassured and planned as elective procedures.(5-7).Staging of breast cancer and diagnosis of metastatic breast cancer at metastatic sites is another use (8).In our own setting where patients frequently present with very advanced cancer often requiring neoadjuvant chemotherapy to reduce the primary tumour load, FNAC is frequently relied on for therapeutic decision making because many patients cannot afford the triple test prescription. The alternative being open biopsy for diagnosis with its attendant high cost and complications. The other worry is the effect on such therapy on the receptor status. Happily Kinsella et al in Atlanta Georgia, studied receptor status in 45 patients pre and post neoadjuvant therapy and found out that there was no significant change in oestrogen ,Progesterone and Her 2/Neu status following the therapy(9).

Often FNAC has been touted as an exceedingly easy procedure requiring no training whatsoever. This not the case as aptly stated by Abu-Salem 2002 'that the accuracy of FNAC depends on the expertise and experience of the Cyto-pathologist and technical skills of the physician performing the procedure'(10).In practice FNAC is highly technical, requiring highly trained multidisciplinary manpower. In planning execution, interpretation and audit, strict benchmarks must be met to bring about high performance.For example in the United Kingdom NHS breast cancer screening programme, published guidelines for Non operative diagnostic procedures of the breast. The last publication in 2001,covers six areas. The six areas are (1)Use of Non operative techniques(2)Sampling techniques and procedures(3) FNAC reporting guidelines (4) Diagnostic pitfalls in interpretation of breast FNAC (5) Core biopsy reporting guidelines and (6) Quality assurance(11). In the developed countries newer procedures such as, Ultrasound guided core needle biopsy(12, 13) and vacuum assisted core biopsy are replacing FNAC(14).Here in Calabar as is in many developing countries there is a compelling need to strengthen the procedure to attain its full potential. Our surgeon colleagues for example, wish we could provide more morphological details in our FNAC reports from which they can take quicker clinical decisions. As part of our response there is now an up scaling in FNAC training and retraining in the department and to know the baseline going forward, we are conducting this audit.

2 MATERIALS AND METHODS

A descriptive retrospective study involving a review of breast cytology reports with matched eventual histological outcome, carried out within 1st January 2012 to 31st October 2014.Both males and females with palpable breast lumps who had FNAC diagnosis followed by open biopsy and histology diagnosis are included in the study. Those excluded are those with palpable breast lumps who did not have the two procedures in the sequence stated above. Both electronic files, manual data and cytology as well as

histological files of corresponding to these patients are sorted out. Also retrieved are archival slides of the cytology and histology of these patients. Some that had undergone photo fading are re-stained for examination. From these files the demographic data including age, sex and laboratory identity numbers were extracted. Other data such as side of breast, presenting symptoms and duration of symptoms were extracted. Both the corresponding cytology slides and histology slides were re-examined and the results revalidated. The data is then fed into IBM statistical package (SPSS) version 21.0 for analysis. Comparison with NHSBSP guidelines was carried out as a quality assurance measure.

3 RESULT

Cytology and their matched histology reports of ninety-three (93) cases of breast masses seen at UCTH within January 2012 and October 2014. The histology diagnosis is assumed to be the gold standard. Only one of the cases (1.07%) was male, yielding a female: male ratio of 1: 0.01. Mean age was 38.0 ± 15.3 years ranging from 10 to 78 years, with 21-30 as commonest age group. The commonest age group for benign disease was also 21-30 years (with mean age of 30.3 ± 12.3 years), while that of malignant disease was 41-50 years (with mean age of 46.3 ± 13.7 years) (Figure 1.1). Only two cases (2.2%) occurred at both breast, with the rest occurring at the right (47, 52.2%) or left (41, 45.6%) breast.

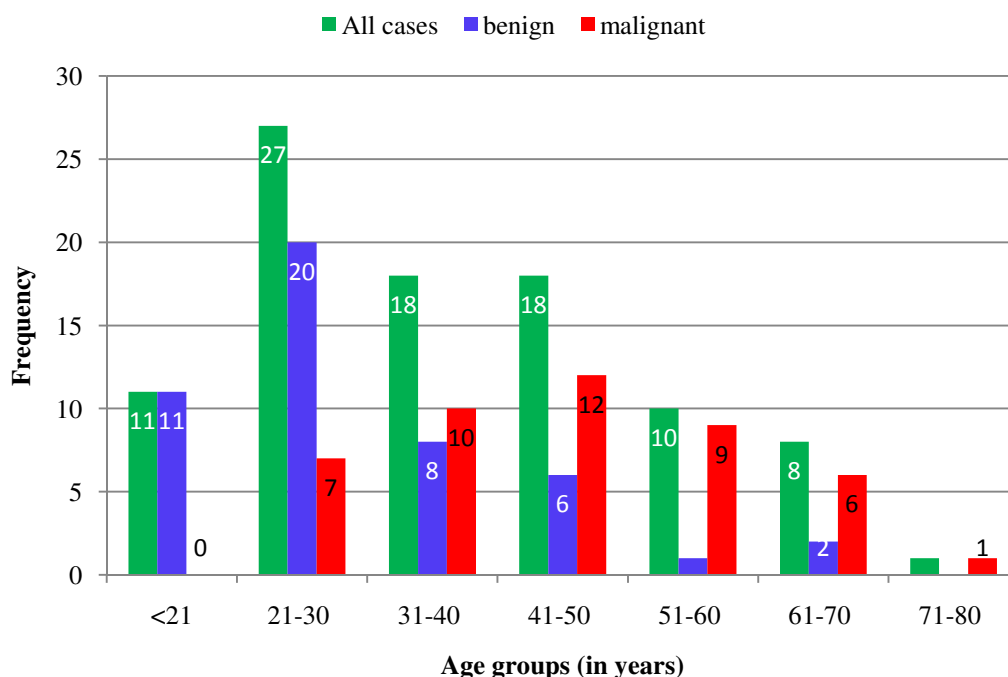


Figure 1.1: Age group distribution of breast masses (N=93)

The commonest cytology report was benign disease (49, 52.7%) consisting of certainly benign (42, 45.2%) and atypical probably benign (7, 7.5%) (table 1). Thirty-six cases (38.7%) were considered

malignant, consisting of certainly malignant (27, 29.0%) and atypical probably malignant (9, 9.7%). Consequently, 45 out of 93 cases of breast masses were malignant, yielding a breast cancer prevalence of 48.39%. Unsatisfactory smears were reported for eight cases (8.6%). Fibroadenoma (21, 43.8%) and fibrocystic change (11, 22.9%) were the common forms of benign histology, with the only male case in the study, being the only case of gynecomastia seen. Invasive ductal carcinoma (41, 91.1%) was the commonest malignant histology (table 1).

Table 1: Cytology and histology report of breast masses (N=93)

Variable	Frequency	Percentage
Cytology (n=93)		
Benign disease (C2)	42	45.2
Malignant disease (C5)	27	29.0
Atypical probably malignant (C4)	9	9.7
Unsatisfactory (C1)	8	8.6
Atypical probably benign (C3)	7	7.5
Total	93	100
Benign histology (n=48)		
Fibroadenoma	21	43.8
Fibrocystic change	11	22.9
Fibrocystic disease with atypical ductal hyperplasia	4	8.3
Periductal mastitis	3	6.3
Fat necrosis	2	4.2
Juvenile papillomatosis	1	2.1
Tubular adenoma	1	2.1
Fibrolipoma	1	2.1
Lipoma	1	2.1
Granulomatous mastitis	1	2.1
Myofibroblastoma	1	2.1
Gynecomastia	1	2.1
Total	48	100
Malignant histology (n=45)		
Invasive ductal (NOS)	41	91.1
Mucinous carcinoma	2	4.4
Medullary carcinoma	1	2.2
Invasive lobular	1	2.2
Total	45	100

Quality of our results was determined by benchmarking our results with the NHSBSP standard as seen in tables 2 and 3. The absolute sensitivity of FNAC was 72.1% (95% CI: 55.3-84.7%), was within the prescribed minimum and preferred limit. Absolute sensitivity being defined as 'the number of carcinomas diagnosed as such (C5) expressed as the total number of carcinomas sampled. Complete sensitivity was 90.7% and this was within the minimum and preferred limits on the NHSBSP standards; complete sensitivity being defined as the number of carcinomas that were not definitely negative or inadequate on FNAC expressed as the total number of carcinomas. The full specificity was 88.1% (95% CI: 74.4 - 96.0%), and this is defined as 'the number of correctly identified benign lesions (number of C2 results minus number of false negatives) expressed as a percentage of total number of benign lesions aspirated, and this was within the recommended limit. The positive predictive value was 86.1% (95% CI: 70.5-95.3%); defined as 'the number of correctly identified cancers (number of C5 minus number of false positive results) expressed as a percentage of the total number of positive result (C5). The outcome was slightly more than ten percentage point short of the NHSBSP benchmark, the minimum being >98% and the preferred >99%. The false negative rate was 24.5% and is defined as 'the number of false negative results expressed as a percentage of the total number of carcinomas sampled'. This was much higher than the NHSBSP benchmark which is <6% minimum and <4% preferred. The inadequate rate was 8.6% and this was lower than <25% minimum and <15% preferred NHSBSP benchmark.

Table 2: Cancer diagnostic characteristics of FNAC (N=93)

Test characteristic	Value
Definite cancer positive test on cytology (A)	36
Definite cancer negative test on cytology (B)	49
Definite cancer positive test on histology (C)	43
Definite cancer negative test on histology (D)	42
Borderline of inadequate/unsatisfactory FNAC (E)	8
True positive (TP)	31
False positive (FP)	5
True negative (TN)	37
False negative (FN)	12
True positive rate	86.1%
False positive rate	13.9%
True negative rate	75.5%
False negative rate	24.5%
Inadequate rate for FNAC (E/N)	8.6%
Complete Sensitivity (TP+E/TP+FN)	90.7%
Absolute Sensitivity (TP/TP+FN)	72.1% (95% CI: 55.3-84.7%)
Full Specificity (TN/TN+FP)	88.1% (95% CI: 74.4 - 96.0%)
Positive predictive value (TP/TP+FP)	86.1% (95% CI: 70.5-95.3%)
Negative predictive value (TN/TN+FN)	75.5% (95% CI: 61.1-86.7%)
Likelihood ratio positive (sensitivity / 1-specificity)	6.06 (95% CI: 2.6-14.1)
Likelihood ratio negative (1-sensitivity / specificity)	0.32 (95% CI: 0.2-0.5)
Accuracy (TP+TN / TP+TN+FP+FN)	80%

Table 3: Comparison of Result with UK NHSBSP Thresholds of Performance.

Parameters Study	Minimum %	Preferred %	UCTH
Absolute Sensitivity	>60	>70	72.1%
Complete Sensitivity	>80	>90	90%
Full Specificity	>55	>55	88.1%
Positive Predictive Value	>98	>99	86.1%
False Negative Rate	<6	<4	24.5%
Inadequate Rate	<25	<15	8.6%

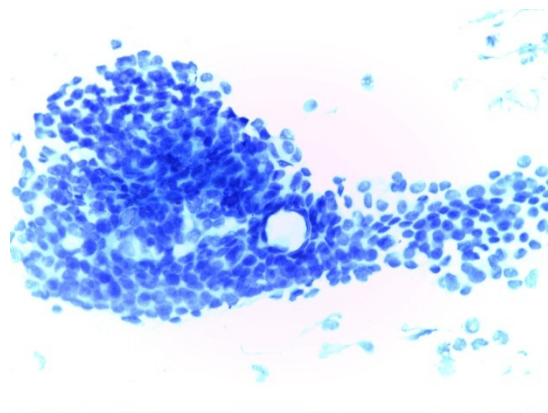


Figure1: FNAC (C2-Benign) PaP X100

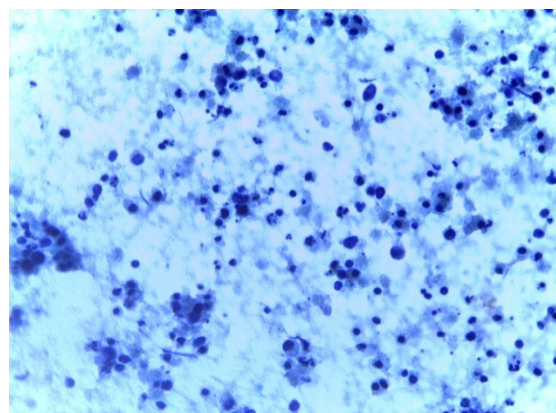


Figure2: FNAC (C3-Atypical Probably Benign) Pap X100

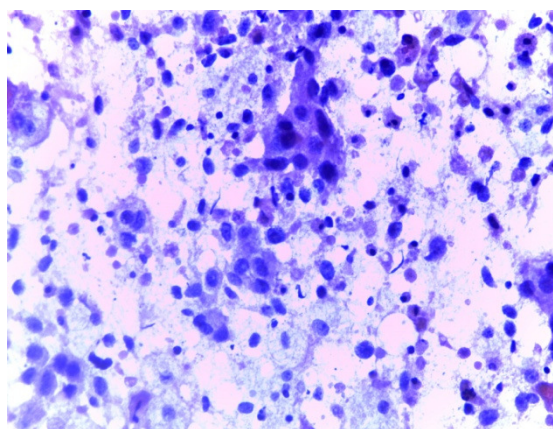


Figure 3: FNAC (C4-Atypical Probably Malignant) PaP X100

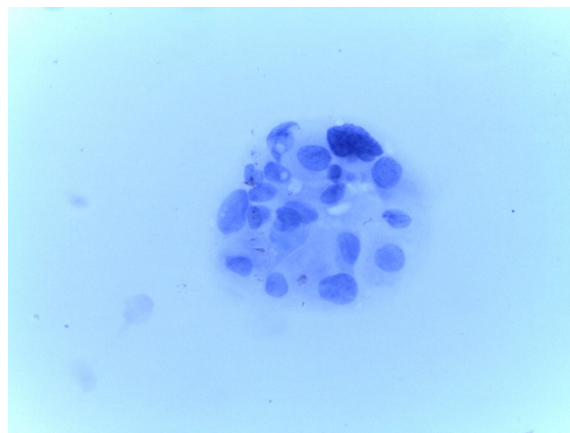


Figure 4: FNAC (C5-Malignant)Pap X 400

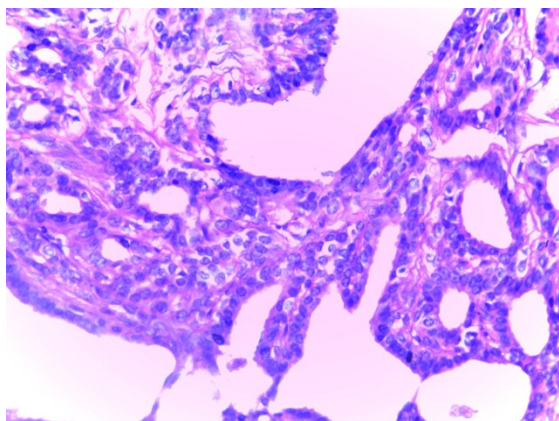


Figure 5: Biopsy Fibrosytic Disease with Atypical Ductal Hyperplasia (H&E X 100)

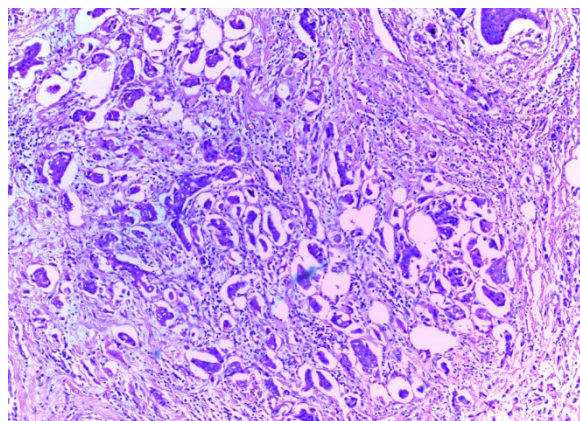


Figure 6: Biopsy Invasive Ductal Carcinoma (H&E X 100)

Of the five cases that were false positive at FNAC, three were reported as C4= Atypical probably malignant at cytology and all the corresponding histological diagnosis were Fibrocystic disease with atypical ductal hyperplasia. The two cases that were C5= Certainly malignant at cytology, their corresponding histological diagnosis were fibrocystic disease with atypical hyperplasia while the other is non proliferative fibrocystic disease. Upon re-examination of these cytological slides, all cases were reviewed to C3=Atypical probably benign and classified as error of interpretation. Twelve cases were false negative, out of these 8 were diagnosed as C2=(Benign).Their corresponding histological diagnosis were 7 invasive ductal carcinoma(Nos) and one medullary carcinoma. Upon re-examination of the cytology slides 7 were classified as sampling error while one (medullary by histology) was classified as interpretation error. The remaining 4 false negatives on FNAC were reported as C3= Atypical probably benign and the corresponding histological diagnosis is invasive ductal carcinoma(nos). On review, all these showed small foci of atypical cells and these were reviewed to C4 probably malignant and they were all judged interpretation error.

4 DISCUSSION:

For FNAC set up to be reliable in a screening programme or in an institution based diagnostic set up, a high performance standard has to be met; the type set by the NHSBSP guideline (11).After more than three decades of carrying out the procedure in Calabar, standardization has become imperative to enable us improve the test performance . Our result show that complete specificity 90.7%,absolute specificity, 72.1% (95% CI: 55.3-84.7%) and full specificity 88.1% (95% CI: 74.4 - 96.0%), met the minimum and preferred benchmarks of NHSBSP(11).Though the values tended to be on the lower side of normal especially when compared to Daramola et al Lagos 2015 who recorded 95.4% absolute sensitivity,99.2 % complete sensitivity, and full sensitivity of 88,9%(15).Of importance is the large number of cases reviewed

by the Lagos group(1790) over a 5 year period. FNAC is one procedure where repeated performance is important in proficiency attainment(16, 17). Equally high performance was reported by Dong et al 2016 in Massachusetts United States (Complete sensitivity 91.6% and specificity of 95.5%) following a review of a sample size of 1654 cases(12).

The test performance did not meet the NHSBSP minimum and preferred positive predictive value of C5 diagnosis (>98% and >99% NHSBSP(11) Vs 86.1% for Calabar).The false positive rate was 13.9% and is much higher than the NHSBSP <1% minimum and <0.1% preferred(11).The five false positive cytology proved on histology to be cases of fibrocystic disease and four of these had atypical hyperplasia and the other was a fibrocystic disease without atypia. Atypical hyperplasia is a known diagnostic pitfall especially in inexperienced hands(16).Because the cytology of lesions with atypical ductal hyperplasia was commonly misdiagnosed as malignancy in Calabar. Attention will hence forth be paid to identifying smears from atypical hyperplasias. Gangopadhyay et al 1997 described the features to include 'three dimensional ductal cell clusters, a swirling growth pattern, sublumens, cell discohesion and conspicuous nuclear overlap as indicative of moderate ductal hyperplasia(18).Ductal atypia they opined should be reported when nuclear features such as anisonucleosis, irregular nuclear membranes, clumped chromatin and eosinophilic macronucleoli are present(18).

The false negative rate was high(24.5% Calabar vs <6% minimum and <4% preferred for NHSBSP(11). Of the twelve smears in the false negative category,8 were judged C2 and 4 were C3.By re examination after their histologies had proven to be malignant 7 of the C2 smears did not contain malignant cells so were classified as sampling errors. One very important reason in Literature why sampling errors occurs is the size of the lump. It is known that FNAC may be unreliable if the size of the invasive lesion is lesion than one centimetre(19). Although in this case we did not encounter such a problem what appears to be the problem is that they existed benign conditions with malignancies and in each of those cases the benign lesions were selectively biopsied. We combed these smears on review for the possibility of the presence of two population of cell as was suggested in NHSBSP guideline(11), yet we could not find the malignant cells. One of the C2 cases on cytology turned out to be medullary carcinoma on histology, that is why the cytology was interpreted as inflammatory smear because it had a lot of lymphocytes. The other four false negative smears were reported as C3(atypical probably benign), upon review they had small foci of very atypical cells which were overlooked. Luckily in all these false negative cases the clinical judgment was used to take decision and the patients were spared the ordeal of having to wait for too long.

5 CONCLUSION:

Fine needle aspiration cytology of the breast as practised in Calabar,is cheap and quick means of diagnosis of breast cancer but its safety and reliability has to be improved upon. Effort must be made to reduce the false positive and false negative rates. In a region where most of the patients cannot afford the

exotic radiological diagnostic investigations, our best bet is to combine clinical examination and FNAC until such a time radiologic investigations and all the new innovations in core biopsies and stereotactic techniques become common place

6 LIMITATIONS OF STUDY: The number of years this study covers are so few equally the various personnel carrying out the procedure for example (Surgeons versus Pathologist) are assessed for individual proficiency.

7 RECOMMENDATION: The whole FNAC process needs to be revaluated and personnel involved in the process should be retrained. Effort must be intensified towards providing large core needle biopsy service to complement fine needle aspiration so as to act as double check in lieu of complementary radiological assessment to effect triple test.

CONSENT: Not applicable.

ETHICAL APPROVAL: Ethical approval was granted by the institution's ethical board to the Calabar breast study group.

REFERENCES.

1. Ghimire B, Khan MI, Bibhusal T, Singh Y, Sayami P. Accuracy of triple test score in the diagnosis of palpable breast lump. JNMA J Nepal Med Assoc. 2008 Oct-Dec;47(172):189-92.
2. Jan M, Mattoo JA, Salroo NA, Ahangar S. Triple assessment in the diagnosis of breast cancer in Kashmir. Indian J Surg. 2010 Apr;72(2):97-103.
3. Kaufman Z, Shpitz B, Shapiro M, Rona R, Lew S, Dinbar A. Triple approach in the diagnosis of dominant breast masses: combined physical examination, mammography, and fine-needle aspiration. J Surg Oncol. 1994 Aug;56(4):254-7.
4. Spalding TJ, Dewar EP, Buchanan JD, Mugridge AR, Conroy B. Fine needle aspiration cytology as part of a three stage diagnostic approach to breast lumps in a District general hospital. J R Nav Med Serv. 1989 Spring;75(1):5-9.
5. Feichter GE, Haberthur F, Gobat S, Dalquen P. Breast cytology. Statistical analysis and cytohistologic correlations. Acta Cytol. 1997 Mar-Apr;41(2):327-32.
6. Halevy A, Reif R, Bogokovsky H, Orda R. Diagnosis of carcinoma of the breast by fine needle aspiration cytology. Surg Gynecol Obstet. 1987 Jun;164(6):506-8.
7. Ingram DM, Sterrett GF, Sheiner HJ, Shilkin KB. Fine-needle aspiration cytology in the management of breast disease. Med J Aust. 1983 Aug 20;2(4):170-3.
8. Kocjan G. [Needle aspiration cytology of the breast: current perspective on the role in diagnosis and management]. Acta Med Croatica. 2008 Oct;62(4):391-401.
9. Kinsella MD, Nassar A, Siddiqui MT, Cohen C. Estrogen receptor (ER), progesterone receptor (PR), and HER2 expression pre- and post- neoadjuvant chemotherapy in primary breast carcinoma: a single institutional experience. Int J Clin Exp Pathol. 2012;5(6):530-6.
10. Abu-Salem OT. Fine needle aspiration biopsy (FNAB) of breast lumps: comparison study between pre- and post-operative histological diagnosis. Arch Inst Pasteur Tunis. 2002;79(1-4):59-63.
11. I. O. Ellis SH, M. Michell, S. E. Pinder, C. A.Wells,, and H. D. Zakhour. Guidelines for Non-Operative Diagnostic Procedures and Reporting in Breast Cancer Screening, NHS Cancer Screening Programme. 2001 June 2001;Publication 50:1-60.

12. Dong J, Ly A, Arpin R, Ahmed Q, Brachtel E. Breast fine needle aspiration continues to be relevant in a large academic medical center: experience from Massachusetts General Hospital. *Breast Cancer Res Treat*. 2016 Jul;158(2):297-305.
13. Abdel-Hadi M, Abdel-Hamid GF, Abdel-Razek N, Fawzy RK. Should fine-needle aspiration cytology be the first choice diagnostic modality for assessment of all nonpalpable breast lesions? The experience of a breast cancer screening center in Alexandria, Egypt. *Diagn Cytopathol*. 2010 Dec;38(12):880-9.
14. ADRIANA BONIFACINO VP, TIZIANA PISANI,, SIMONE GIANNERINI AG, ALDO VECCHIONE,, GIOVAGNOLI PLMaMR. Accuracy Rates of US-guided Vacuum-assisted Breast Biopsy. *ANTICANCER RESEARCH*: . [Original article]. 2005; 25:2465-70.
15. Daramola AO, Odubanjo MO, Obiajulu FJ, Ikeri NZ, Banjo AA. Correlation between Fine-Needle Aspiration Cytology and Histology for Palpable Breast Masses in a Nigerian Tertiary Health Institution. *Int J Breast Cancer*. 2015;2015:742573.
16. Kline TS, Joshi LP, Neal HS. Fine-needle aspiration of the breast: diagnoses and pitfalls. A review of 3545 cases. *Cancer*. 1979 Oct;44(4):1458-64.
17. Zakowski MF. Fine-needle aspiration cytology of tumors: diagnostic accuracy and potential pitfalls. *Cancer Invest*. 1994;12(5):505-15.
18. Gangopadhyay M, Nijhawan R, Joshi K, Gupta S. Cytology of "significant" breast ductal proliferations. *Acta Cytol*. 1997 Jul-Aug;41(4):1112-20.
19. Kerin MJ, McAnena OJ, Waldron RP, McGuire M, Given HF. Diagnostic pitfalls of fine needle aspiration cytology for breast disease. *Ir Med J*. 1993 May;86(3):100-1.