A Comparative Study on Fine Needle Aspiration Cytological and Histopathological Findings in Clinically Palpable Breast Lumps

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I. Introduction

Most recent data from GLOBOCAN 2018 suggests that breast cancer which is the most common cancer among women in the world, is also now most common cancer in India among both sexes and also among women. Almost 1,62,468 new cases of breast cancer are diagnosed every year in India which amounts to 28% of cancers among women. Approximately 87,000 women are estimated to die of breast cancer every year, indicating a high case fatality ratio [1].The incidence in many developing countries like India has been increasing at a more rapid rate than in developed countries and breast cancer in these countries is often associated with poorer survival [2]. Of the breast cancer deaths around the world in 2002, more than 50% occurred in countries with limited resources [2]. This is largely due to late presentation of the disease, limited resources for diagnosis and treatment in these places[2]. In 2005, the Breast Health Global Initiative stratified levels of resources in countries with limited resources (from lowest to highest) into basic, limited, enhanced and maximal [3]. In these countries, the economic realities appear to force physicians to support a paradigm shift away from sophisticated, expensive and invasive modes of investigation in favor of cheaper, readily available, minimally invasive, yet reliable methods [4].

FNAC has been adopted worldwide and has been proven to be safe, simple, fast, and cost-effective if properly performed [5–8] with a quality cytopathology service. With FNAC, it is possible to make "one-stop" diagnosis at outpatient clinics. However, the success of FNAC requires not only an excellent aspirator to obtain satisfactory aspirates but also breast cytopathological expertise in interpreting the breast aspirates [9–11]. Its accuracy in many situations when applied by experienced and trained practitioners can approach that of histopathology in providing equivocal diagnosis [12]. FNAC has superseded the use of frozen section examination in the diagnosis and management of patients with breast cancer [13]. Immunocytochemical staining(ICC) performed on FNA smears using Cell Transfer technique is reliable for assessment of Hormonal receptors and Her-2 status of breast cancers, especially when the direct smears are highly cellular[14].Accuracy of FNAC can be increased by multiple sampling or image guidance [15].

Breast lump is the most common presentation of breast diseases. Most accepted protocol followed for breast lumps is "triple assessment", which includes clinical assessment, radiological imaging and pathological diagnosis. Since FNAC forms the most important aspect of cytopathology as a part of triple assessment it is expected to be an efficient technique which can be relied upon in terms of avoiding further diagnostic procedure before proceeding to final definitive surgery.

II. Material And Methods

This prospective study included 50 females of the age group above 15 years selected randomly, having a breast lump (in one or both the breasts), who attended the surgical OPD and were admitted in our department of General Surgery, at Guru Gobind Hospital, affiliated to M. P. Shah Medical College, Jamnagar, Gujarat, during the period of December 2015 to March 2017 with following eligibility criteria:

A. Inclusion Criteria:
a. Age above and equal to 15 years
b. Palpable breast lump
c. Patient without any previous breast lesions, any invasive procedures or treatment of any kind for the same breast lump

B. Exclusion Criteria
a. Patient not willing for written consent
b. Inflammatory breast cancer
c. Previously diagnosed or treated cases of any malignancy
d. Radiation therapy given to the breast
e. Acute inflammatory conditions of the breast
f. Male patients with breast lump

Patients presenting with the complaint of breast lump were assessed as follows:
1. Clinical breast examination of the breast lump
2. Ultrasonography (local) of both the breasts and axilla
3. Fine needle aspiration cytology (FNAC) of breast mass
4. After FNAC report, benign breast lesions subjected to excisional biopsy and malignant lesions subjected to Modified Radical Mastectomy with prior written consent of patient and her relative.
5. Specimen was shown to the relatives and sent for histopathological examination.
6. A correlational study was made between the FNAC and the histopathological findings of excised specimen of definitive surgery and statistical analysis was done.

Equipments:
1. Needles: Fine-gauge number 23 single-use disposable needles were used in the study in all patients as a strict protocol.
2. Syringes: Regular 10 cc single-use disposable plastic syringes were used for aspirating the material from the breast lumps.
3. Slides: 4 dry clean slides were used for preparing the smears. All slides were labelled with a glass pencil and air-dried.

Fixatives: As a routine, all smears were fixed with 95% alcohol.

Stains: All the slides were stained with Papanicolaou (PAP) stain.

Technique:
After taking a written consent, the patient was explained of the procedure in complete detail in vernal language. The procedure was performed without any local anesthesia in the Pathology Department of Guru Gobind Hospital, Jamnagar.
The skin over the suspicious area was cleaned with spirit, the lump was held by hand and stabilized. With the plunger retracted, many passes were made in the lump till sufficient material was seen in the needle hub. Air was aspirated in the syringe and after attaching the needle again the aspirated material was sprayed on the glass and smears were made.The smear was fixed with 95% alcohol and later stained with PAP stain.The slides were then observed under microscope and graded accordingly.Cytology reports were interpreted as benign, malignant, suspicious and uninterpretable. Statistical analysis for correlation of FNAC and the histopathological findings of excised specimen of definitive surgery was done. The statistical tests used in the interpretation of the results obtained in our study were the determination of:

Sensitivity of FNAC as a diagnostic procedure for the entire study
Specificity of FNAC in relation to the malignant lesions
PPV of FNAC as a diagnostic procedure for the entire study
NPV in relation to the malignant lesions

In our study, out of the 50 patients who underwent FNAC, in 48 cases the FNAC report matched the final histopathology report. Thus there were 48 true positives, 2 false negatives and no false positives and true negatives in our study.

The **Sensitivity** of a test is the ability of a test to identify correctly all those who have the disease. In our study the sensitivity would be:

Sensitivity = true positives/true positives + false negatives *100
=48/50*100
=96%

The **Specificity** of a test is the ability of the study to identify correctly the candidates who do not have the disease.

In our study, only females with a lump in their breast were selected. Therefore, in purely statistical terms, there were no normal individuals i.e. those women with normal breasts were not selected. Hence, the ability of FNAC as a diagnostic test to identify correctly those individuals not having disease i.e. true negatives, could not be calculated since in every patient in our study, FNAC would reveal some result.Hence, to give a wider spectrum to our interpretation of the results, we calculated the specificity of FNAC for malignant lesions against benign lesions i.e. "how specific is FNAC as a test in the diagnosis of malignancy in a breast lump?"

Table 1: Correlation of FNAC and the Histopathological Examination Findings

HPE / FNAC	MALIGNANT	NON-MALIGNANCY	TOTAL
MALIGNANT	31	0	31
NON-MALIGNANT	2	17	19
TOTAL	33	17	50

Specificity = true negatives **/** true negatives + false positives * 100
= 17/17+0 * 100
= 100%

The **Positive Predictive Value** of a test indicates the probability that the patient with a positive test has, in fact, the disease in question.

Positive Predictive Value = true positives / true positives + false positives * 100
= 48 / 48+0 * 100
= 100 %

It should be noted that in this study positive predictive value is for FNAC as a diagnostic test for all patients.

The **Negative Predictive Value** of a test indicates the probability of a patient with a negative test not having the disease in question.

As stated previously, we had no true negatives. In the absence of true negatives, the negative predictive value of test is actually zero, since the numerator becomes zero. As with the calculation of specificity for malignant lesions, we broadened the interpretation of our results by calculating the negative predictive value of the test for malignant lesions.

Negative Predictive Value = true negatives / true negatives + false negatives * 100
= 17 / 17+2 * 100
= 89.47%

III. Results

As shown in Table II, out of the 50 patients, 17(34%) patients had benign breast disease and 33(66%) patients had breast carcinoma. Majority Benign breast diseases were found in 15-29 years of age group. Above 30 years, only 2(4%) patients had benign breast disease out of which 1 cases was of fibrocystic breast disease at the age of 50 years and 1 patient with benign phyllodes tumour at the age of 60 years. All 33 breast carcinoma cases in our study were observed at or after 30 years of age with maximum cases between 35-44 years [8(16%) cases in 35-39 years age group and 7(14%) cases in 40-44 years age group].

Table II: AGE DISTRIBUTION OF CASES

AGE INTERVAL (IN YEARS)	MALIGNANT	BENIGN	TOTAL	% OF CASES
15-19	-	4	4	8
20-24	-	5	5	10
25-29	-	5	5	10
30-34	3	-	3	6

35-39	8	-	8	16
40-44	7	-	7	14
45-49	4	-	4	8
50-54	4	2	6	12
55-59	4	-	4	8
60-64	1	1	2	4
65-69	1	-	1	2
70-74	1	-	1	2
TOTAL	33	17	50	100
% OF CASES	66	28	100	

Table III shows 46(92%) out of 50 patients had one or the other signs or symptoms along with breast lump. 9(18%) patients had pain and tenderness out of which 2 were benign (1 case was of chronic inflammation with fat necrosis and other was of fibroadenoma) and 7(14%) were malignant cases. 17(28%)patients had nipple retraction, all of which were found to be malignant. 2(4%) cases had skin changes (peau'd orange) all of which were malignant. 17(28%) cases were associated with lymphadenopathy out of which 2 were benign (cases of chronic inflammation) and 15 were malignant. Fixity to chest wall was seen in only 1(2%) case which was a malignancy (Table III).

Table III: Different Signs and Symptoms seen in patients apart from breast lump

CLINICAL FEATURES	BENIGN	MALIGNANCY	TOTAL	% OF CASES
PAIN/TENDER-NESS	2	7	9	18
FEVER	-	-	-	0
NIPPLE RETRACTION	-	17	17	34
SKIN CHANGES	-	2	2	4
LYMPHADENOPATHY	2	15	17	34
FIXITY TO CHEST WALL	-	1	1	2
TOTAL	-	-	46	92

As shown in table IV, out of 33 malignant cases, maximum cases i.e. 31 (93.9%) were found to be Invasive Ductal Carcinoma, 1(2%) case was of Ductal Carcinoma In Situ (DCIS) and 1(2%) of malignant phyllodes tumor. FNAC and histopathological findings matched in 48 out of 50 cases and differed only in 2 cases in which 1 case was detected as Fibrocystic disease on FNAC and was found to be Invasive Ductal Carcinoma on HPE (histopathological examination) and the second case detected was as Benign Phyllodes Tumor on FNAC which turned out to be Malignant Phyllodes Tumor on HPE.

Table IV : Correlation between FNAC and Histopathological Findings

PATHOLOGY OF BREAST LUMP	FNAC FINDINGS	HISTOPATHOLOGICAL FINDINGS
FIBROADENOMA	6	6
FIBROCYSTIC DISEASE	6	5
BENIGN PHYLLODES TUMOR	5	4
MALIGNANT PHYLLODES TUMOR	0	1
INFLAMMATION	2	2
INVASIVE DUCTAL CARCINOMA	30	31
DCIS	1	1
TOTAL	50	50

The statistical analysis of the study showed that the sensitivity and PPV of FNAC for all patients is 96% and 100% respectively. The specificity and NPV of FNAC for malignancy is 100% and 89.47% respectively. There were no suspicious or uninterpretable reports observed in our study.
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IV. Discussion
A breast lump is a common presenting complaint in the surgical outpatient department and is accompanied with a great degree of anxiety with the fear of malignancy. Hence a quick diagnosis of a breast lump is essential. Criteria such as cost effectiveness, use of anesthesia, duration of procedure, time between the diagnostic procedure and the report, patient's comfort and hospital stay, cosmetic outcome, absence of false positive results and most importantly, reliability in deciding subsequent treatment, are all factors to be taken into account in this regard. Considering all these points, FNAC is ideal initial diagnostic modality for breast lumps .All 50 selected patients underwent FNAC and patients who did not follow up after the procedure were not included in the study. Every patient included in this study was admitted and underwent a definitive surgical procedure as demanded by the FNAC report. The results obtained were tabulated and conclusions were drawn based on statistical analysis. The most important aspect of this study was to draw conclusions regarding the correlations of cytopathological and histopathological findings in these patients. Our study did not attempt to

draw any conclusions as to whether one diagnostic modality could replace the other. Estrogen receptor (ER), progesterone receptor (PR), and Her2-neu expression status, and histological grading are potential prognostic indicators of breast carcinoma[16].Although, a core needle biopsy (CNB) is considered the 'gold standard' for assessing the receptor status by immunohistochemistry (IHC), performing IHC on CNB is more time consuming than immunocytochemistry (ICC) on fine-needle aspirates (FNAs)[17].Thus, CNB remains an alternative rather than a substitute for FNAC[18]. Also FNA is minimally invasive in comparison to CNB. Moreover, FNAC grading of breast carcinoma has shown to be an useful parameter in assessing the aggressiveness of breast cancer and deciding neoadjuvant chemotherapy.[19,20]. In our present study, sensitivity, specificity, PPV and NPV of FNAC is 96%,100%, 100% and 89.47% respectively. Similar results were also observed in other similar studies shown in table V below:

Table V: Comparison of Sensitivity, Specificity, PPV and NPV of FNAC in different studies

Name of Study	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Present study	96	100	100	89.5
Hebbar AK et al [21]	93.1	100	100	90.5
Rubin et al [22]	87	100	100	89
Ariga 2 et al [23]	98	97	99	86
Bhagat et al [24]	96.4	100	100	93.4
Vijaybharathi et al [25]	97.2	98.7	97.2	98.3
Paramesh et al [26]	95.45	100	100	97.06
Colloco et al [27]	92.1	98.1	99.4	98.1
Bharambe et al [28]	97.6	99.3	97.6	99.3

Occasional complications of FNAC include the formation of a hematoma, post procedural pain and rare chance of tumor seedling along the needle tract. With needles used now being fine, this chance is even less likely. However there are few limitations in terms of its inability to diagnose lesions if the aspirate is scanty either due to inexperienced operator or inexperienced cytopathologist. In relation to breast pathologies there are obvious advantages in the form of very few false positives in differentiating between benign and malignant lesions, as well as of being diagnostic and therapeutic in most breast cysts. The conditions that have a risk of a false positive result are papillary lesions, atypical epithelial hyperplasia, recurrent epithelial atypical and atypia of ductal epithelium in a cyst. Also invasive and in-situ ductal carcinomas are not always distinguishable on FNAC alone.

V. Conclusion:

FNAC is a patient friendly, easy, reliable, repeatable and simple diagnostic test.A high sensitivity and high PPV proved that a positive finding of FNAC in the breast means a definite diagnosis of the concerned pathology if compared with the final HPE findings.The high specificity and high NPV for malignancy illustrated the high accuracy of FNAC in the diagnosis of malignancy in the breast. A report negative for malignancy was highly accurate in predicting an absence of malignancy. Thus, without any hesitation we conclude that FNAC is a very important preliminary diagnostic test in palpable breast lumps and if done by experienced hands and with proper technique, the results show a high degree of correlation with HPE findings.

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Abbreviations:
FNAC-Fine Needle Aspiration Cytology
HPE-Histopathological Examination
PPV -Positive Predictive Value
NNV-Negative Predictive Value
ICC-Immunocytochemical
PAP-Papanicolaou
CNB-Core Needle Biopsy
IHC- Immunohistochemistry