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Original Article

A Study on the Clinicopathological, Molecular (Beta-hCG), Sonological Study, and Correlation in Breast Diseases

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Abstract

Introduction: Breast is important organ of female as a symbol of womanhood and fertility. This study is done to know utility of ultrasonography in identifying breast diseases as mammography not routinely available in all treating centres. Role of BetahCG in breast diseases.

Materials and Methods: This is a prospective observational study consisting of 112 patients with breast diseases planned for surgical management from June 2016 to June 2018 and a cyto-sono-histopathological correlation done. Pre-operative evaluation included history, clinical examination, ultrasonography (USG) breast, serum beta-human chorionic gonadotropin (hCG), and post-operative histopathology.

Results: The most common benign lesion was fibroadenoma (62 cases) followed by gynecomastia disease – 5 cases (7.33%). The most common malignant lesion reported in the study was invasive ductal carcinoma – 53 cases. In this study, sensitivity and specificity of breast fine-needle aspiration cytology (FNAC) were 87.5% and 100%, respectively. The diagnostic accuracy of FNAC in our study was reported to be 96.5%. Sensitivity and specificity of breast USG were 84.8.5% and 96.5%, respectively. The diagnostic accuracy of USG in our study was reported to be 93.3%. In our study, a 98.9% cyto-histopathological correlation was observed for benign lesions and 100% for cases suspicious of malignancy. A cyto-histopathological correlation was 100%.

Conclusion: Study concludes that sonography should be the first investigation to be done after the clinical examination because if USG says the disease is benign then the patient can be assured without any invasive procedure, i.e., FNAC and biopsy. If USG says abnormality then the patient should go for an invasive procedure. As far as for early definitive diagnosis, FNAC is superior to Sonology. Serum beta-hCG has no correlation with breast diseases.

Key words: Breast diseases, Fine-needle aspiration cytology, Histopathology, Serum beta-human chorionic gonadotropin, Sonology

INTRODUCTION

The breast has been a symbol of womanhood and ultimate fertility. Being superficially placed in the body has prompted interest of surgeons since the earliest period in the history of medicine. Cosmetic consideration and feel of mutilation have hampered in the early diagnosis of carcinoma breast. Breast is found in both sexes but it is rudimentary in males and for females, the mammary gland is a unique organ which is not fully formed at birth, undergoes cyclical changes during reproductive life. It develops into an important accessory organ of the female reproductive system and child nursing. A few breast diseases occur during reproductive life while some occur during the menopausal period indicating the relation of these diseases to hormonal stimulation as a causative factor.[1]

Breast is a modified sweat gland, comprising of glandular, fibrous, and fatty tissue. It became spot for various lesions

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ranging from mastitis to invasive carcinoma, over a wide range of age. Differentiation of inflammatory and benign lesions from early carcinoma becomes very important, especially in women susceptible to carcinoma of breast.

Most of the benign epithelial lesions are named by many pathologists with variety of terminologies such as cystic disease, fibrocystic disease, cystic mastitis, cystic mastopathy, epithelial hyperplasia, mammary dysplasia, and benign breast disease.[2] Besides, fine-needle aspiration cytology (FNAC) of breast, biopsies, and mastectomy specimens is frequently sent for histopathological examination (HPE). Many of the breast lesions are clinically suspected as malignant lesions but diagnosed as benign after HPE. The varied pattern of benign breast lesions draws our attention to study them in detail with the help of available clinical and radiological data. Since the most important prognostic factor at the time of presentation is the extent of the disease, it is imperative that a definitive preoperative diagnosis is established as early as possible with a view to institute proper treatment and reduces the mortality rates. In recent years, mammary cytology has been contemplated as an effective means of early diagnosis of breast masses.[3]

The combination of fine-needle cytology, clinical examination, and mammography has been suggested as a triple test for the pre-operative diagnosis of breast masses.[4] The advantage of these cytological procedures lies in the evidence that they are simple to perform, cost-effective, rapidly accepted by the patient, and cosmetically least disfiguring. This more rapid diagnostic approach assists to allay the anxiety caused by delays in scheduling, performing, and interpreting an open biopsy.

Cancer of breast is the most common cancer affecting women worldwide and is the second most common cause of cancer death next to lung cancer.[5]

It traditionally presents as a lump or nipple discharge.[6]

"Lump" in breast is, therefore, a cause of great anxiety both to the patient and family members. The main motive behind the evaluation of such a newly detected palpable lump is basically to rule out malignancy. Evaluation of breast lumps includes the rational use of a detailed history, clinical breast examination, imaging modalities, and tissue diagnosis. Although the final diagnosis is made by HPE of the excised tissue, routine excision of all breast lumps would not be rationale, because as much as 80% of lumps are benign.[7]

Thus the requirement of less invasive and cost effective method(s) of diagnosis without applying a more painful and invasive surgical biopsy. The modality should also be acceptable to the patient, accurate, easy to apply, reproducible and must not need too much preparations.[6]

Given the common occurrence of breast cancer and the importance of accurately diagnosing a clinically palpable breast lump, with non-invasive techniques without routinely resorting to formal biopsy which is much invasive, the study is proposed to evaluate the accuracy of ultrasonography (USG) and FNAC in the diagnosis of newly detected clinically palpable breast lumps in comparison to the final HPE report of the biopsied specimens.

Breast lumps are one of the common complaints/cases reported which necessitate early diagnosis, treatment, and work up. Breast cancer is the most constant among women with an estimated 1.67 million new cases diagnosed in 2012 (about 25% of total cancer). It is now the most common cancer in both developed (794,000 cases) and developing regions (883,000 cases). Incidence rate varies from 27 per lac women in Eastern Africa to 98 per lac women in Western Europe. The range of mortality rate is similar, approximately 6–20 per lac, because of the more favorable survival of breast cancer cases in developed countries. As a result, breast cancer rank as the fifth cause of death from cancer but it is still the most frequent cause of cancer death in women in developing regions.[8]

It is estimated that during the year 2012, about 144,937 new cases of breast cancer in women occurred in India, which accounts for 27% of all malignant cases (an incidence rate of 25.8 per lac population). About 70,218 women died of this cancer, mortality rate being 12.7 per lac population, ranking number one killer in women.[8]

A benign diagnosis allows surgery to be avoided in the majority of cases, while a positive diagnosis of carcinoma allows pre-operative discussion with the patient and proper treatment planning with minimal morbidity.[9]

Breast carcinoma is the leading cause of death in females all over the world. About 6% of all women may suffer from carcinoma breast at any point during their lifetime.[9] Carcinoma of the breast can present in several pathological forms across several age groups though it is a commoner there have been several areas of controversy surrounding its presentation and management.

Human chorionic gonadotropin (hCG) is a glycoprotein secreted by placental trophoblasts. Previous studies showed that hCG could be responsible for the pregnancy-induced protection against breast cancer in women. It is reported that hCG decreases proliferation and invasion of breast cancer MCF-7 cells. hCG can decrease the

proliferation of MCF-7 cells by downregulating the expression of proliferation markers, proliferating cell nuclear antigen, and proliferation-related Ki-67 antigen. Interestingly, we learn here that hCG elevates the state of cellular differentiation, as characterized by the upregulation of differentiation markers, β-casein, cytokeratin-18, and E-cadherin. Inhibition of hCG secretion or luteinizing hormone/hCG receptors synthesis can weaken the effect of hCG on the induction of cell differentiation. In addition to this, hCG can suppress the expression of estrogen receptor-alpha. hCG activated receptor-mediated cyclic adenosine monophosphate/protein kinase a signaling pathway. These findings are suggestive of a protective effect of hCG against breast cancer probably corresponding with its growth inhibitory and differentiation induction function in breast cancer cells.[10]

It is in this context that our study has been designed and carried out which will focus on the correlation of various diagnostic modalities which are prerequisites for early diagnosis and treatment of breast diseases and correlation of beta hCG with breast diseases. Appropriate literature review and analysis using standard statistical tests would be used to arrive at conclusions, the details of which are mentioned below.

MATERIALS AND METHODS

The protocol was approved by the local ethics committee and written informed consent was obtained from each patient. This is a prospective observational study consisting of 112 patients with breast diseases planned for surgical management from June 2016 to June 2018 and a cyto-sono-histopathological correlation done. Pre-operative evaluation included history, clinical examination, USG breast, serum beta-hCG, and post-operative histopathology.

Table 1: Age-wise distribution of cases

Age group (in years)	Number of cases	Percentage
14–25	40	35.7
25–35	18	16.1
35–45	26	23.2
45–55	14	12.5
55–65	8	7.1
>65	6	5.4
Total	112	100.0

RESULTS

Results and Analysis

To ensure uniformity in the diagnostic reporting, The National Cancer Institute (NCI) (NHS Breast Screening Programme 2001)[11] has developed and recommended five categories for assessing and reporting of palpable breast lesions. The five categories for reporting of these lesions are: Inadequate smear (C1), benign (C2), suspicious probably benign (C3), suspicious probably malignant (C4), and malignant (C5).

The statistical analysis showed high sensitivity (87.5) and specificity (100%) of FNAC in breast lesions, with positive predictive value (PPV) and the negative predictive value (NPV) being 100% and 95.4%, respectively. The diagnostic accuracy was found to be 96.5%.

The statistical analysis showed high sensitivity (84.8) and specificity (96.5%) of FNAC in breast lesions, with PPV and the NPV being 90.3% and 94.3%, respectively. The diagnostic accuracy was found to be 93.3% [Tables 1-15].

DISCUSSION

FNAC of breast lumps is an accepted and established method for determining the natures of breast lumps with a high degree of accuracy.[12,13] Application of FNA for the diagnosis of palpable breast masses was first introduced by Martin and Ellis in 1930, and since then, it has been established as an important tool in the evaluation of breast lesions.[4] It has been reported in the literature that the incidence of tumor transplantation along the needle track by FNA procedure is only about 0.0045%, and even much lower in superficially located tumors.[14] FNA is widely accepted as a reliable technique in the initial

Table 2: Distribution of benign and malignant cases according to age groups

Age group (in years)	Number of cases (benign)	Percentage	Number of cases (malignant)	Percentage
11–20	19	17	0	0
21–30	29	25.89	0	0
31–40	25	22	3	2.68
41–50	7	6.25	8	7.14
51–60	2	1.79	12	10.71
61–70	1	0.89	4	3.57
Above 70	1	0.89	1	1.79
Total	84	75.00	28	25.89

Table 3: Gender-wise distribution of cases

Sex	Number of cases	Percentage
Male	5	4.5
Female	107	95.5
Total	112	100

Table 4: Site of breast involved among the cases

Site involved	Number of benign	Number of malignant	Number of cases	Percentage
Left breast	29	15	44	39.3
Right breast	46	13	59	52.7
Bilateral	9	0	9	8.0
Total	84	28	112	100

Table 5: Type of quadrant involved among the cases

Quadrant involved	Number of cases	Percentage
Upper outer	51	45.5
Upper inner	18	16.1
Lower outer	13	11.6
Lower inner	11	9.8
Central	13	11.6
Diffuse	6	5.4
Total	112	100

Table 6: Tumor size-wise distribution of cases

Tumor size (in cm)	Number of cases	Percentage
1–2	3	2.6
2–5	87	77.7
5–10	17	15.2
>10	5	4.5
Total	112	100

Table 7: Cytological spectrum of breast lumps on fine-needle aspiration cytology

Cytological diagnosis	Number of cases	Percentage
C1 (inadequate)	9	8
C2 (benign)	75	67
C3 (atypia probably benign)	4	3.57
C4 (suspicious probably malignant)	6	5.35
C5 (malignant)	18	16.1
Total	112	100

evaluation of palpable breast lumps. It is simple, safe, cost-effective, minimally invasive, rapid, and as sensitive as biopsy[15-17] primary goal of FNA is to separate benign lesions from malignant lesions for the purpose of planning the therapeutic protocol and uneventful follow-up.[18-20] In the present study, 300 cases were studied and cytological examination was done using 22 or 24 gauge disposable needles, measuring 1.5" in length and 10 ml disposable syringes without holders.

Table 8: Distribution of malignant lesions

Cytological diagnosis	Number of cases	Percentage *n*=112
Suspicious of malignancy (C4)	6	5.35
Ductal carcinoma *in situ* (C5)	15	13.3
Invasive ductal carcinoma-not otherwise specified (C5)	3	2.67
Total	24	21.32

Table 9: Radiological spectrum of breast lumps on sonography

Sonological diagnosis birads	Number of cases	Percentage
0 (incomplete)	0	0
I (normal)	1	0.89
II (benign)	67	59.8.
III (probably benign)	14	12.5
IV (suspicious abnormality)	18	16
V (malignant)	11	9.8
VI (proven malignant)	1	0.9
Total	112	100

Age and Sex Distribution of Cases

In the present study, the age of the patients ranged from 14 to 85 years with mean age of 38.93 years (standard deviation-16.32). The study population comprised 107 female and 5 male cases. The oldest case (85 years) was diagnosed as gynecomastia and the youngest (15 years) was a fibroadenoma. The most common age group was 31–40 years comprising 83 cases (27.7%). In this study, the maximum numbers of cytologically benign lesions were seen in the age group ranging from 11 to 40 years. In the present study, the range of age of the breast carcinoma cases was 25–70 years. We observed a maximum incidence of breast cancer in the age group of 41–50 years (37.1%). Above 60 years, it was 10% and only 8.6% between 21 and 30 years. Between the age group of 31 and 40 years and 51 and 60 years, frequency of breast cancers is 22.5% and 21.4%, respectively. This is similar to study done by Afsharfard *et al.*[21] and Chopra *et al.*[22]

This was similar to the findings by Khemka *et al.*[22] and Rocha *et al.*[23] who had maximum cytological benign cases in the age groups of 15–44 years and 14–40 years, respectively. MacIntosh *et al.*[24] had majority of benign cases in the age group of 27–77 years. Malignant lesions were common in the age group of 31–70 years in the present study, 35–84 years in the study by Khemka *et al.*[22] 63–79 years in the study by MacIntosh *et al.*[24] and 41–75 years in the study by Rocha *et al.*[23] Hence, overall pattern of occurrence is as expected, with benign lesions were more common in younger age group and malignant lesions in older age group. Similar age group distribution of benign and malignant cases was observed in studies done in Asian countries.[24,25] Higher age group in Western countries was attributed to higher life

Table 10: Summary of statistical analysis of cytology

Cytological diagnosis	Histopathogical diagnosis		Total	*P*-value by Chi-square
	Malignant (positive)	Benign (negative)		
Positive for malignancy (malignant)	24 (TP) (a: True positive)	0 (FP) (b: False positive)	25	<0.05
Negative for malignancy (benign)	4 (FN) (c: False negative)	84 (TN) (d: True negative)	87	
Total	28	84	112	

True positive cases (TP)=24 False positive cases (FP)=00, True negative cases (TN)=84 False negative cases (FN)=04

$$\text{Sensitivity} = \frac{TN}{TP+FN}\times 100 = \frac{24}{24+04}\times 100 = 85.7\%$$

$$\text{Specificity} = \frac{TN}{TN+FP}\times 100 = \frac{84}{84+0}\times 100 = 100\%$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP}\times 100 = \frac{24}{24+00}\times 100 = 100\%$$

$$\text{Negative predictive value} = \frac{TN}{TN+FN}\times 100 = \frac{84}{84+4}\times 100 = 95.4\%$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN}\times 100 = \frac{24+84}{24+0+4+84}\times 100 = 96.4\%$$

Table 11: Statistical results of cytology

S. No.	Statistical indices	Result (%)
1.	Sensitivity	87.5
2.	Specificity	100
3.	Positive predictive value	100
4.	Negative predictive value	95.4
5.	Diagnostic accuracy	96.5

expectancy.[26] Khemka *et al.*[22] observed that benign lesions of breast were more commonly seen in younger age groups with maximum number of patients found in the age group of 30–34 years. Ganiat *et al.*[25] reported a maximum number of patients with malignant lesions in the age group from fourth to seventh decade of life.

In India, the average age of developing breast cancer has shifted over the past few decades and younger women (40–50 year) are being affected. Epidemiological studies suggest that this cancer occurs at a younger premenopausal age in Indian and Asian women compared to western women who get it more than a decade or more later.

The lifestyle factors such as late age at marriage, reduced breast feeding, and westernization of diet may be associated with occurrence of breast cancer in younger population in India. Early menarche and late menopause also increase risk of disease. India may face a potential breast cancer epidemic over the next decades as women adopt western lifestyles, marrying, and bearing children later in life, decreasing parity, shorter duration of breastfeeding, and change in dietary habits.[21]

Most of cases (98.6%) were females. Only five case male but all of them are benign. No male breast cancer found in this study period, this finding somewhat is similar to Shet *et al.*[27] who found 1.6% of male breast cancer in total breast cancer cases.

Breast cancer is about 100 times less common among men than among women. For men, the lifetime risk of getting breast cancer is about 1 in 1000.

Site and Location of Breast Involvement among the Cases

In our study, 68.6% cases had left side breast cancer and 31.4% cases had right side breast cancer, which is similar to studies by Moses Ambroise *et al.* who reported 59.2% cases in left breast. The observation that breast cancer is more common in the left than the right breast has been of interest to the medical community for at least 50 years. A satisfactory explanation for the excess incidence of left breast cancers has not yet been elucidated.

In our study, most common location involved was upper outer quadrant (57.1%). Second common location was subareolar (32.9%), followed by lower inner, lower outer, upper inner 5.7%, 2.9%, and 1.4%, respectively. This is similar to study done by Lee.[28]

The marked difference in the carcinoma frequency depending on the quadrant matches closely to the amount of breast parenchyma in each quadrant.

Out of 112 cases studied, 44 cases (39.3%) were in left breast, 59 cases (52.7%) were in right breast, and 9 cases (8%) presented bilaterally. Hussain[25] reported left breast involvement in 27 patients (54%) and right breast involvement in 23 cases (46%) and concluded that left breast was involved more commonly than right. Meena *et al.*[29] Reddy and Reddy,[30] and Clegg-Lamptey and Hodasi[31] also studied that palpable breast lesions on the left side were slightly more common.

Among all four quadrants, upper and outer (superolateral) quadrant was the most commonly involved quadrant (54.33%) in the present study with 112 cases. This is in agreement with the findings of other studies such as Rocha *et al.*[32] (45.20%), Zuk *et al.*[33] (42.20%), Reddy and Reddy *et al.*[30] (54.20%), Meena *et al.*[29] (54%), and Clegg-Lamptey and Hodasi *et al.*[31] (42.40%). The exact cause of this finding is not known. Hussain *et al.*[15] and Khemkha *et al.*[11] also

Table 12: Summary of statistical analysis of Sonology

Sonological diagnosis	Histopathogical diagnosis		Total	*P*-value by Chi-square
	Malignant (positive)	Benign (negative)		
Positive for malignancy (malignant)	28 (TP) (a: True positive)	03 (FP) (b: False positive)	31	<0.05
Negative for malignancy (benign)	5 (FN) (c: False negative)	84 (TN) (d: True negative)	89	
Total	33	87	150	

True positive cases (TP)=28 False positive cases (FP)=03, True negative cases (TN)=84 False-negative cases (FN)=05

$$\text{Sensitivity} = \frac{TP}{TP+FN} \times 100 = \frac{28}{28=05} \times 100 = 84.8\%$$

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100 = \frac{84}{84+03} \times 100 = 96.5\%$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP} \times 100 = \frac{28}{28+03} \times 100 = 90.3\%$$

$$\text{Negative predictive value} = \frac{TN}{TN+FP} \times 100 = \frac{84}{84+5} \times 100 = 94.3\%$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN} \times 100 = \frac{28+84}{28+03+05+84} \times 100 = 93.3\%$$

Table 13. Statistical indices of sonography

S. No.	Statistical indices	Result (%)
1.	Sensitivity	84.8
2.	Specificity	96.5
3.	Positive predictive value	90.3
4.	Negative predictive value	94.3
5.	Diagnostic accuracy	93.3

observed upper and outer quadrant as the commonest site. Swapan and Ranjana.[34] determined the topographic distribution of different breast lesions and observed that the left breast was found to be more common site of malignancy and the upper outer quadrant being the most common site.

All the 112 aspirations were subjected to cytological study lesions were classified into five diagnostic classes, to ensure uniformity in the diagnostic reporting, the NCI has developed and recommended five categories for assessing and reporting of palpable breast lesions.[35] The five categories for reporting of these lesions are: Inadequate smear (C1), benign (C2), atypia probably benign (C3), suspicious probably malignant (C4), and malignant (C5).

In the present study of 112 patients, 84 cases were benign cases (76.66%), and malignant lesions were found in 28 cases (21%). Yeoh and Chan[36] studied 1533 breast masses on FNAC and found that 70.4% cases were benign. Similarly, Ganiat *et al.* studied 757 cases on FNAC and found that maximum number of cases was benign (50.2%), Malik *et al.*[36] in his study of 1724 cases over a period of 20 years reported benign lesions in 72.97% and malignant lesions in 27.3% of cases. Similar results were obtained by Iyer[37] and Mayun *et al.*[38] A difference was noted in the incidences of benign and malignant breast lesions amongst various studies, which may be explained on the basis of variables such as the duration of study period, number of cases studied, and age group of patients.

It has been emphasized in the past that vast majority of the lesions in breast are benign.[39-42] Aslam *et al.*[43] also documented fibroadenoma as the most common benign lesion (71.3%) in their study. López-Ferrer *et al.*[44] stated that FA may be accompanied by changes such as atypical multinucleated giant cells and mild epithelial atypia, which may lead to an erroneous diagnosis of malignancy.

Another common benign breast lesion we encountered was fibrocystic change with 2 cases (1.7%) which was characterized by sheets of ductal epithelial cells of apocrine type and scattered single bipolar nuclei in the background of variable amount of cyst fluid and macrophages. More than 90% of the fibrocystic change were non-proliferative. Compared to the general population, proliferative fibrocystic change with or without atypia has relative risk of developing carcinoma. Other benign and cystic lesions encountered were simple benign cysts with 1 cases (0.89%), gynecomastia 5 cases (4.4%), and benign phyllodes tumor 2 cases (1.7%). Inflammatory lesions accounted for 3 cases (2.7%), which included cases of chronic inflammatory cells along with ductal epithelial cells showing regenerative atypia, 1 cases of granulomatous mastitis, and 1 cases of chronic mastitis. In the present study, 1 case (5.66%) showed epithelial hyperplasia, 2 cases of lipoma, fat necrosis, and duct ectasia each. Six cases of breast lump on cytology showed lactational changes and 1 case of duct papilloma was also seen in the study population.

Breast cancer is the second most common cancer among Indian females next only to cervical cancer. In experienced hands, FNA is highly accurate diagnostic procedure with sensitivity and specificity over 95% for palpable breast lesions.[45,46] In the present study, 18 cases (16.1%) were positive for malignancy with maximum incidence of carcinoma and were found in 51–60 years (12 cases). Out of 18 malignant lesions, 15 cases were diagnosed as ductal

Table 14: Comparison of cytological findings of the present study with the various other studies

Studies	Total cases	Benign cases, *n* (%)	Atypical cases, *n* (%)	Malignant cases, *n* (%)	Suspicious cases, *n* (%)	Unsatisfactory cases, *n* (%)
Feither *et al*.[76]	1472	1003 (68.1)	12 (0.8)	239 (26.6)	169 (11.5)	49 (3.3)
Khan *et al*.[77]	74	24 (32.4)	03 (4.1)	41 (55.4)	06 (8.1)	0 (0)
Yusuf *et al*.[78]	200	109 (54.5)	20 (10)	44 (22)	27 (13.5)	0 (0)
Panjvani *et al*.[53]	222	150 (68.18)	01 (0.45)	69 (31.08)	02 (0.90)	00 (00)
Chokshi *et al*.[79]	407	293 (22.59)	08 (1.96)	70 (17.19)	08 (1.96)	28 (6.87)
Present study	112	75 (67)	4 (3.5)	18 (16.1)	6 (5.35)	9 (8)

Table 15. Comparison of overall diagnostic accuracy of FNAC in breast lesions

S. No.	Study	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
1.	Silverman *et al*.[80]	96	100	100	98	99
2.	Sampat *et al*.[81]	96	100	100	89.5	97
3.	Rocha *et al*.[23]	93.80	98.21	92.70	95.6	97.4
4.	Choi *et al*.[82]	77.7	99.2	98.4	88	91.1
5.	Pinto *et al*.[58]	97.8	100	100	98.6	99.1
6.	Joshi *et al*.[83]	96.97	100	100	98.63	99.1
7.	Present study	87.5	100	100	95.4	96.5

FNAC: Fine-needle aspiration cytology

Table 16: Distribution of breast lesions

Category	Histopathological diagnosis	Number of cases	Percentage *n*=112
Inflammatory lesions (3 cases-2.7%)	Zuska disease	1	0.89
	Granulomatous mastitis	1	0.89
	Chronic mastitis (non-specific)	1	0.89
Benign breast lesions (72 cases-61.24%)	Fibroadenoma	62	55.3
	Fibrocystic change	2	1.7
	Tubular adenoma	2	1.7
	Simple cyst	1	0.89
	Epithelial hyperplasia	1	0.89
	Gynecomastia	5	4.4
Lesion not recognized as benign or malignant	Phyllodes tumor	2	1.7
Miscellaneous	(Lipoma, keratin cyst)	6	5
Carcinoma		28	25
Total		112	100

carcinoma. Singh *et al*.[47] reported that invasive ductal carcinoma is the most common breast malignancy and found in the age group of 41–60 years of age.

Out of 112 cases studied for cytology, histopathology was available for 112 cases which were operated in K.J. Somaiya Hospital. Of the 18 FNAC positive for malignancy cases, the histopathology follow-up of 18 cases was available as only these patients underwent surgery for breast cancer in this institute. (We took only patient which underwent surgery).

In the present study, there were 88 cases diagnosed under the benign category from which 88 cases were available for histological follow-up. Out of these 88 confirmed cases, 84 cases were found to be benign while four case was found to be malignant (false-negative case). One false-negative case which was seen in the lactating female whose cytology was diagnosed as giant fibroadenoma, its further follow-up on histopathology was found out to be infiltrating ductal carcinoma.

The false-positive FNAC results can be reduced by considering biopsy in such cases, especially when the aspirate yields poor cellularity shows presence of bare nuclei and lesser degree of atypia.[48]

In this prospective study, 112 cases were included for cytohistologic correlation with 88 (78.5%) benign cases, 18 (16%) malignant cases, and 6 (5.3%) cases reported as suspicious of malignancy. Among the benign cases fibroadenoma comprised the maximum cases (35) followed by breast carcinoma in 24 cases. In the present study, 6 cases which were cytologically diagnosed as lesions suspicious for malignancy, of which 6 were confirmed as malignant lesions on HPE, however. No case was diagnosed as benign. Cytohistologic correlation was seen in 95.4% of benign cases and 100% in cases suspicious for malignancy.

All the 18 cytologically diagnosed malignant cases were confirmed as malignant on subsequent HPEs. Hence, in our study, a 100% cyto-histopathological correlation was observed for malignant lesions Qin *et al*.[49]

AZ Mohammed *et al*.[50] and Tiwari[6] had also observed the similar results in their studies. Other studies also noted an increase in rate of malignancy on histopathology in lesions which were previously diagnosed under the category of "suspicious lesions for malignancy." Comparison of cytohistological correlation in various studies is shown in Table 16.

Suen and Chan *et al*.[51] in their study stated that the PPV for malignancy should be >95% with a false-positive rate of <1% and false-negative rate of <5%. In present study, the PPV for malignancy was 100% with no false-positive case which meets the criteria mentioned by Suen.

Bell *et al*.[52] had stated that aspiration cytology was accurate, rapid and of value in the assessment and management of patient in office practice. Documentation of the presence of breast cancer by FNAC might obviate the need for a two stage procedure in the surgical management of breast cancer. In our institution also FNAC is being used as basic test for surgical management of malignant breast lesions; after surgery the whole specimen is submitted for HPE and confirmation of malignancy.

Panjvani *et al*.[53] studied 222 patients, 217 were females and 5 were males. Benign breast lesions were found in 144 cases (64.87%); among which fibroadenoma (30.18%) was the commonest lesion which was observed. Malignancy was observed in 69 cases (31.08%); among them, infiltrating ductal carcinoma was the predominant lesion (29.28%) which was seen. Histopathological confirmations were obtained in 91 cases, in which histocytopathological corrections were possible. All 45 malignant aspirates were confirmed by histopathology. Benign reports were confirmed in 45 out of 46 cases by doing histological examinations; except one case which was diagnosed as malignant by studying its histopathology. Sensitivity and specificity of FNAC in breast lesions were reported to be 97.82% and 100%, respectively, with 100% PPV and 97.85% NPV.

Diagnostic accuracy of FNAC in the present study was found to be 98.9%. These findings were comparable to the findings in our study.

Monika *et al*.[54] studied that a total of 128 cases were studied which included 101 benign cases, 21 malignant cases, and 6 inadequate cases. The final 122 cases included, 44 cases (36.1%) of fibroadenoma, there were 21 cases (17.21%) of ductal carcinoma. Majority of benign cases were between 30 and 39 years of age group (43.6%). Majority of malignant cases fell between 50 and 59 years of age group (47.6%). Majority (61.5%) of lumps (>3 cm) were malignant, whereas 94.8% of lumps (<3 cm) were benign. Left breast was commonly involved (49.18%) than the right breast (44.26%). Superolateral quadrant (63.1%) was the most commonly involved quadrant. The findings were similar to the findings in our study.

Halevy *et al*.[55] have stated that to achieve good results, three rules must be borne in mind. First, a trained cytopathologists should perform the FNAC and interpret the result. Second, close cooperation between surgeon and cytopathologists is necessary. Finally, a negative FNAC finding does not rule out a malignant condition.

Yeoh and Chan[36] in their study reported six cases as false negative which include one heavily blood stained smear that had mixed cytological features, which was interpreted as a cyst, two misdiagnoses due to well differentiated tumors in the benign category, and three cases that were reported as atypical. False-negative diagnosis might be due to technical failure, misdiagnosis, or the presence of mixed benign and malignant cytological features. Technical failure include acellular or insufficient cellular material, heavily blood stained smears, partial air drying, and smearing artifact resulting in cell disruption.

Ariga *et al*[56] performed 1158 FNAs on women being evaluated for a clinically palpable breast masses. The patients were divided into two groups. Group I consisted of 231 patients aged 40 years and younger and Group II consisted of 927 patients aged 41 years and older. In Group I, there were 117 (51%) malignant FNA diagnosis and only 1 (1%) false-positive case, subsequently diagnosed on histopathological material as an atypical papillomatosis. There were 20 (9%) cases diagnosed as suspicious on FNA. On histopathology, 10 were malignant and 10 were benign. Of the 91 (3%) cases interpreted as benign, only one was false-negative. In Group II, which comprised 927 patients, there were 693 (74%) malignant FNA diagnosis and 3 (<1%) false-positive cases, which on follow-up HPE revealed two atypical ductal hyperplasia and one atypical papilloma. For cases suspicious on FNA, 90 (10%) were diagnosed. On histopathology, 68 were malignant and 22 were benign. Of the 131 (14%) lesions interpreted as benign, there were 18 false-negative cases (14%) which included 17 infiltrating carcinomas and one DCIS. For the study, 12 (1%) cases were inadequate. Group I had 99% sensitivity, 99% PPV, 99% specificity, 99% NPV. Group II had 98% sensitivity, 97% specificity, 99% PPV, and 86% NPV. These results were comparable with the results of our study.

Ishita *et al*.[57] performed 125 FNAs of breast over a period of 1 year. Of these 60 cases were followed-up by

histopathologic confirmation. The diagnostic accuracy of this series was assessed. The sensitivity of the FNA procedure was 93.10%, specificity 97.06%, with a PPV 96.43%. The overall diagnostic accuracy was 95.24%. The present study shows comparable results with sensitivity 98.3%, specificity 98.9%, and diagnostic accuracy of 98.7%.

Pinto *et al.*[58] did 58 FNAs of the breast with subsequent histopathology. The youngest patient was 12 and the oldest was 82. Females comprised 555 (95.4%) and males 27 (4.6%). Out of 582 aspirations, 295 cases (50.7%) were negative (benign) on cytology and in 107 cases (18.4%) the smears were inconclusive and biopsy was advised. Fibroadenoma (188 cases) was the most common benign neoplasm. The cytohistologic correlation was 89.7% for fibroadenoma, 65.2% for fibrocystic change, 60% for benign phyllodes tumor, 57.1% for fibroadenosis, and 33.3% for breast abscess.

The present study confirms the view that FNAC has high ability to detect benign and malignant lesions with high efficacy and accuracy. Thus, FNAC of breast is a sensitive and specific modality in diagnosing breast lesion and in management of the breast lesions.

Breast carcinoma has been reported in only 4% of patients with breast symptoms, and even among palpable lesions undergoing biopsy, a large number of lesions turned out to be benign.[59,60] The role of mammography in patients with palpable breast lumps is to show a benign cause for palpable abnormality and to avoid further intervention, to support earlier intervention for a mass with malignant features, screen the remainder of the ipsilateral and contralateral breast for additional lesions, and to assess the extent of malignancy when cancer is diagnosed.[61] However, the false-negative rate of mammography for breast cancer in patients with palpable abnormalities of the breasts has been reported to be as high as 16.5%.[62] Multiple studies have shown that the false-negative rate for a combined mammographic and sonographic evaluation varies from 0% to 2.6%.[63,64] Additional imaging with sonography is appropriate in most instances, with the exception of lesions that are mammographically benign as noted above or lesions that are highly indicative of malignancy, in which sonographic imaging would not add any additional information. Sonography may obviate the need for intervention by showing benign causes of palpable abnormalities such as cysts, benign intra mammary lymph nodes, extravasated silicon, and superficial thrombophlebitis of Mondor disease of the breast.

In this study, 20 (40%) of the 50 lesions were categorized as benign after sonographic evaluation, clearly showing the value of imaging in helping avoid unnecessary biopsies. In these patients, sonography was able to categorize palpable lesions obscured by dense tissue on mammograms. Moss *et al.*[51] reported that sonography increased cancer detection by 14% in symptomatic patients who were evaluated with both mammography and sonography. In retrospective analysis of 293 palpable malignant lesions, sonography detected all cancers; 18 (6.1%) of these 293 cancers were mammographically occult. In study of 411 palpable abnormalities by Shetty and Shah, 66 (16%) of the 165 palpable abnormalities were mammographically occult. In this study, one lesion (fat necrosis) was sonographically occult and was visualized only on mammography. Seven (14%) of the 50 lesions were mammographically occult and were seen only on ultrasound. Of these 6 were benign cysts and one was duct ectasia. Sonography therefore is complimentary to mammography in patients with palpable abnormalities; its superiority over mammography is in being able to show lesions obscured by dense breast tissue and in characterizing palpable lesions that are mammographically visible or occult. Mammography is complimentary to sonography because of its ability to screen the reminder of the ipsilateral and contra lateral breast for clinically occult lesions. It has been reported that the accuracy of sonography is comparable with that of mammography as a screening modality for breast cancer. However, the role of sonographic screening for additional lesions in the symptomatic patients has not been reported.

Combined imaging evaluation leads to fewer unnecessary biopsies. Perdue *et al.*[60] reported that only 11.1% of 623 excisional biopsy specimens of palpable breast revealed carcinoma.[39] In this study, only 7 of the 50 palpable abnormalities underwent biopsy on the basis of imaging findings and only 2 (4%) showed malignancy.

In a review article, Donegan[57] stated that most of the breast cancers appear as palpable masses, usually found by the patient. However, not all palpable abnormalities represent discrete masses. This is especially true in women younger than 40 years in whom normal glandular nodularity may be mistaken for dominant masses.[65] In this study, 50 patients who presented with palpable abnormalities 23 patients showed negative findings sonographic examination. Nine of these patients underwent biopsy on the grounds of clinical suspicion and all were benign. Of 411 palpable abnormalities studied by Shetty and Shah 186 cases showed negative findings, clearly showing the importance of imaging.

A small number of palpable masses detected on physical examination are malignant; in this study, 4% of the palpable lesions that underwent combined mammographic and sonographic imaging were cancer, compared with 5% in a series of 123 cases of palpable breast thickening reported by Kaiser *et al.*, 5% in 605 patients younger than 40 years

reported by Marrow *et al.*, and 17% in 750 breast lesions reported by Stavros *et al.*

The value of combined mammographic and sonographic imaging in symptomatic patients has been studied previously. Moss *et al.* reported sensitivity of 94.2% and specificity of 67.9% in 368 patients. Shetty and Shah reported a sensitivity of 100% and specificity of 80.1%. Barlow *et al.* reported a sensitive of 87% and specificity of 88% and PPV of 22%.[66]

Their findings are comparable with present findings of sensitivity of 84.8% and specificity of 96.5% in patients with palpable breast lumps.

Heterodimeric placental HCG and ectopically expressed β-HCG have opposing effects on breast cancer development. The reasons for these contrary effects are still controversial. One explanation could be the glycosylation state of HCG, finding that hyperglycosylated β-subunits of HCG promote cancer cell invasion, growth, and metastases. Another cause for the differing effect of HCG on breast cancer cells could be the fact that the *LHCGR* carries a large number of polymorphisms. As a consequence, sensitivity and plasma membrane expression can be changed, leading to different receptor activity. Moreover, *HCG* genes also carry many polymorphisms which lead to expression of different HCG types. All these points can cause opposing effects on breast cancer development and could explain controversial data at least partially. The protective effect of placental HCG on the mammary gland led to the hypothesis that mimicking pregnancy might be a strategy for breast cancer prevention. In contrast, the tumor-promoting β-HCG expressed in breast cancer cells seems to be a promising target for immunological approaches of breast cancer therapy.[67]

The majority of previous studies clearly suggests a protective or inhibitory action of heterodimeric placental HCG on breast cancer development, though other studies could not find such an effect. In animal models, administration of hCG reduced risk of carcinogen-induced breast cancer, an effect which was mediated by induction of apoptosis and elevated inhibit expression.[68-70]

Various studies reported a negative correlation between serum HCG levels and breast cancer risk. Russo *et al.* found that high levels of HCG during the 1st weeks of pregnancy reduced the incidence of maternal breast cancer rate after the age of 50.[71] Toniolo *et al.* reported a risk reduction of about 30% of getting breast cancer when women had higher HCG levels in the first 3 months of pregnancy.[72] Lukanova *et al.* found that women with HCG levels in the top tertile tended to be at lower risk of breast cancer than women with HCG levels in the lowest tertile.[73] No such inverse relationship between early pregnancy serum HCG concentrations and breast cancer risk was found by other studies including in a recent large prospective study from Finland including 1191 women with invasive breast cancer and 2257 controls.[74] In another study, young nulliparous women receiving injections of HCG for weight loss or infertility treatment were reported to have a slightly decreased risk for developing breast cancer.[75]

The beneficial effect of HCG was supported by the results of two studies examining the effect of treatment with recombinant HCG. In a placebo-controlled study, postmenopausal women with primary breast cancer diagnosed by core biopsy were treated with HCG or a placebo for 2 weeks. After this period, therapeutic mastectomies or lumpectomies were performed. Tissue examinations demonstrated that the proliferative cell index was decreased from 18% to 4% in the HCG-treated group, suggesting that this hormone is able to inhibit breast cancer cell proliferation.[49]

Contradictory to other studies we found that there is no correlation of serum beta-hCG with breast diseases. Serum beta-hCG neither protective nor promotive factor for breast disease

CONCLUSION

Use of sonography plays an important role in the management of palpable breast lesions. Its applications are.

- Characterizes the palpable mass lesion.
- Avoids unnecessary interventions in which imaging findings are unequivocally benign.

Negative findings on sonographic imaging have very high specificity and are reassuring to the patient.

FNAC is a patient friendly, easy, reliable, repeatable, and simple diagnostic test. When performed by an expert pathologist, the diagnostic accuracy of FNAC is very high. A high sensitivity and a high PPV proved that a positive FNAC in the breast means a definite diagnosis of the concerned pathology if compared with the final histology report. The high specificity and a high NPV for malignancy illustrated the high accuracy of FNAC in the diagnosis of malignancy in the breast. Very importantly, a report negative for malignancy was highly accurate (>98%) in predicting an absence of malignancy. Thus, we conclude that FNAC is a very important preliminary diagnostic test in palpable breast lumps. Adhering to the principle of triple test, with the acquisition of technical, observational, and interpretative skills will further enhance the diagnostic

accuracy of lesions of the breast.

Over all our study concludes that sonography should be the first investigation to be done after clinical examination because if sonography says disease is benign then patient can be assured without any invasive procedure, i.e., FNAC and biopsy. If sonography says abnormality then patient should go for invasive procedure. As far as, for early definitive diagnosis FNAC is superior to Sonology. Serum beta-hCG has no correlation with breast diseases.

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