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Comparative study of core needle biopsy with excisional biopsy: To determine diagnostic accuracy & concordance with er/pr/her-2/neu status

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Abstract

Background: As there is continuous and increased need for early detection of cancer in breast lesion is never-ending. It is so, as the success of treatment depends upon early diagnosis. So role of core needle biopsy (CNB) in screening and diagnosing the breast lesion was evaluated.

Aims and Objectives: To find concordance between the diagnostic power of, hormonal receptors, *viz.* estrogen receptors (ER), progesterone receptors (PR) sensitivity along with expression of HER-2/neu in CNB and excisional biopsy (EB) of breast lesion.

Materials and Methods: We have studied the diagnostic accuracy of CNB in 60 breast lesion keeping the EB as gold standard. Immunohistochemical study (IHC) was simultaneously performed with three parameters as ER, PR and HER-2/neu. The results IHC studies of CNB were compared with the same study on EB specimens.

Results: Out of which 39 cases were malignant and amazingly CNB has detected the malignancy in 38 cases. Also the IHC of ER, PR and HER-2/neu were well in concordance with the same study in EB specimen.

Conclusion: Though CNB is excellent modality for screening, as study reflects, it can surely be used for confirmation also. As IHC results on CNB are also in well concordance with EB, the oncologist can lay out his treatment from very initial step of screening.

Keywords: Core needle biopsy (CNB), Excisional biopsy (EB), Estrogen receptor (ER), Progesterone receptor (PR) and HER-2/neu.

Introduction

Diseases of breast constitute a significant proportion of surgical cases and need early differentiation between benign and malignant lesions, prior to definitive treatment. Triple assessment (clinical examination, imaging and fine needle aspiration cytology-FNAC) was a useful modality, but still not definitive. Therefore an accurate, easy to perform and reproducible method of definitive diagnosis of patients who presents with breast lumps at outpatient clinic is strongly needed.[17]

Much concern is given to malignant lesions of breast as according to W.H.O. breast carcinoma constitutes 22% of all female cancers. Although breast cancer incidence continues to increase, death rate from breast cancers has declined significantly in last few years due to earlier detection and more effective treatment modalities.[14]

CNB was introduced in late seventies, since then has become an important diagnostic tool in the assessment of palpable and non-palpable breast lesions. The results were more encouraging with the introduction of automated core gun and its combination with image guidance).[3] It was reported to have a sensitivity of around 90% and specificity of 100%.[5,11,13] In one study, there was excellent correlation between CNB and EB in the diagnosis of benign and malignant breast lesions.[6] FNAC does not differentiate between in situ and invasive breast carcinoma, but it can be documented by CNB.[10,16] Grading and typing of tumours and is also possible on CNB, thereby increasing diagnostic information available when considering treatment options.[16] CNB also provides all the information necessary for decision making in the management of breast cancer and its accuracy is higher than FNAC.[9] In triple assessment of breast lumps, replacing FNAC with automated core biopsy is recommended as superior diagnostic power.[4]

In recent years, interest in prognostic factors has been stimulated by the success of systemic adjuvant therapy for early stage of cancer of breast.[19] Intracellular steroid hormone receptor protein, primarily ER and PR have received intensive study both as an indicator of prognosis and as guide to hormone therapy. The clinical importance of ER and PR relates principally to the fact that its presence identifies hormone sensitive tumour. Patients with ER positive tumours have a prolonged disease free survival after primary treatment compared with patients which are negative for ER.[1,19] As CNB is now increasingly used for preoperative assessment of breast lesions, there is an increasing need to provide prognostic data on CNB in order to improve treatment outcome.[8,12] In a study, higher concordance rate between CNB and EB for ER (95%) than PR (89%) has been observed and it has also showed that CNB has sensitivity of 97% for ER and 95% for PR. Finally it has been concluded that preoperative CNB is highly sensitive for immunohistochemical detection for ER and PR in invasive breast cancer.[18]

In HER-2/neu positive breast cancer, tumor cells have abnormally high number of HER-2/neu gene per

cells which cause cancer cells to grow and divide more quickly and so is considered more aggressive.[15] Besides this, women with Her-2/neu positive breast cancer have more chances of recurrence. Also the treatment of HER-2/neu positive breast cancer is entirely different from treatment of HER-2/neu negative breast.[7]

Material and Methods

A total of 60 patients studied on whom CNB was carried out as pre planned to evaluate the type of breast lesions and the diagnosis so made was compared with their histopathological findings after EB as a diagnostic gold standard. Both CNB and EB specimen were processed routinely and stained with H&E. The immunohistochemical staining for ER, PR and HER-2/neu were done CNB and EB sections using primary monoclonal antibodies (Biogenics kit). Findings of CNB were recorded and categorized into following groups based on NHSBSP June 2001 guidelines

B1: Normal tissue/unpredictable
B2: Benign
B3: Benign but of uncertain biological potential
B4: Suspicious
B5: Malignant: (a) In situ; (b) Invasive; (c) Uncertain

The CNB as well as EB sections were further processed for immunohistochemical detection of Hormone Receptor *i.e.* ER/PR and HER-2/neu overexpression. Histopathological findings as well as immunohistochemical examination of CNB specimens were analysed correlated with findings of EB sections to calculate sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), suspicious, false negative rate (FNR), false positive rate (FPR), inadequate CNB rate for cancers, suspicious rate, core biopsy miss rate for cancers and concordance. (Table 3)

In all cases of breast malignancy immunohistochemical scoring for ER and PR was done by Quick scoring method as devised by Allred et al.[1] For HER-2/neu overexpression status DAKO scoring system was applied.[2]

Observation

Table 1: Distribution of cases according to EB diagnosis

Diagnosis	No. of cases/ (percentage)	
A. Inflammatory Lesions 1. Granulomatous mastitis (GM) 2. Tubercular (TB) mastitis	01(1.7%) 01(1.7%)	Benign 21(35%)
B. Benign neoplastic lesions 1. Fibroadenoma (FA) 2. Fibrocystic disease (FCD) 3. Fibroadenosis (FAD)	14(23.3%) 03(5.0%) 02(3.3%)	
C. Malignant neoplastic lesions 1. Inv. ductal carcinoma(IDC) 2. Inv. lobular carcinoma (ILC) 3. Inv. papillary carcinoma (IPC) 4. 4. Medullary Carcinoma (MC)	36(60.0%) 01(1.7%) 01(1.7%) 01(1.7%)	Malignant 39(65%)
Total	60	

Out of 60 cases 21(35%) cases were benign and 39(65%) cases were malignant lesions of breast after EB examination. In benign cases, maximum number of cases were of fibroadenoma 14(23.3%) followed by fibrocystic disease 03(5.0%), fibroadenosis 02(3.3%), granulomatous mastitis 01(1.7%), and tubercular mastitis 01(1.7%) while in malignant lesions most cases *i.e.* 36(60.0%) were of invasive ductal carcinoma followed by invasive lobular carcinoma 01(1.7%), invasive papillary carcinoma 01(1.7%) and medullary carcinoma 01(1.7%) (Table 1).

Table 2: Correlation of CNB (b-categorisation) and EB diagnosis

CNB		EB		Total
B-Catg.	**Cases (%)**	**Benign (%)**	**Malignant (%)**	
B1(Normal tissues/ unpredictable)	02(3.33%)	01(1.66%)	01(1.66%)	02
B2 (Benign)	20(33.33%)	20(33.33%)	00(0%)	20
B3 (Benign, but of uncertain biological potential)	00(0%)	00(0%)	00(0%)	00
B4(Suspicious for malignant)	03(5.0%)	00(0%)	03(5.0%)	03
B5(malignant)	35(58.3%)	00(0%)	35(58.3%)	35

The patients included in our study underwent CNB procedure and its finding were categorized (B-catg.). After categorization 2 cases (3.3%) were in B1(normal tissue/ unpredictable), 20 cases (33.3%) in B2(benign), nil cases (0%) in B3 (benign but of uncertain biological potential), 03 cases (5.0%) in B4 (suspicious) and 35 cases (58.3%) in B5 (malignant). To avoid confusion in correlation with excisional biopsy, we've considered B1, B2 & B3 in benign category and B4 & B5 in malignant category. (Table 2)

Table 3: Calculated values of various parameters for CNB

Parameters	Our results (%)CNB
Absolute sensitivity	89.7
Complete sensitivity	97.4
Specificity	100
NPV	95.4
PPV(B5)	100
PPV(B4)	100
PPV(B3)	00
FNR	2.56
FPR	00
Inadequate CNB rate from cancer	2.56
Suspicious rate	7.69
Core biopsy miss rate for cancer	2.56

Table 4: Comparative evaluation of specific typing on CNB & EB diagnosis

CNB			EB								
			Benign					Malignant			
B-catg.		Total Cases	FA	FC	FAD	GM	TM	IDC	ILC	IPC	MC
B1(02)	Benign (22)	02	01	--	--	--	-	01	--	--	--
B2-FA		14	13	01	--	--	--	--	--	--	--
B2-FCD		02	--	02	--	--	--	--	--	--	--
B2-FAD		02	--	--	02	--	--	--	--	--	--
B2-GM		01	--	--	--	01	--	--	--	--	--
B2-TM		01	--	--	--	--	01	--	--	--	--
B3		--	--	--	--	--	--	--	--	--	--
B4	Malignant(38)	03	--	--	--	--	--	02	--	01	--
B5-IDC		33	--	--	--	--	--	33	--	--	--
B5-MC		01	--	--	--	--	--	--	--	--	01
B5-ILC		01	--	--	--	--	--	--	01	--	--
Total		60	14	03	02	01	01	35	01	01	01

On comparing CNB with EB diagnosis 2 inadequate cases of B1 category turned out to be as 1 case of fibroadenoma and another invasive ductal carcinoma. Of 3 case of B4 in which no specific diagnosis can be made, when compared found that 2 case turned out to be invasive ductal carcinoma and one case as invasive papillary carcinoma on EB. So in benign (B1, B2 & B3), correct typing was made in 19/22 cases while in malignant lesions (B4 & B5), correct typing was done in 35/38 case. (Table 4)

Study of immunohistochemistry (ER, PR & HER-2/neu) in malignant breast lesions

The immunohistochemical staining for ER, PR & HER-2/neu were performed on all 39 cases in EB sections as well as EB sections and a comparative study was performed in between.

Table 5: Comparative study of HER-2/neu receptor status in CNB and EB in malignant breast lesions

Result	Excisional biopsy (No. of cases)	Core needle biopsy (No. of cases)	Total positive cases by both CNB and Excisional biopsy	Total negative cases by both CNB & Excisional biopsy
ER-Positive	18(46.16%)	17(43.5%)	17(43.5%)	-
ER-Negative	21(53.84%)	22(56.5%)	-	21(53.84%)
PR-Positive	16 (41.0%)	12(30.8%)	12(30.8%)	-
PR-Negative	23 (59.0%)	27(69.2%)	-	23 (59.0%)
HER-Positive	09(23.0%)	06(15.4%)	06 (15.4%)	-
HER-Negative	30(77%)	33(84.6%)	-	30(77%)

Among 39 cases studied for ER, PR and HER-2/neu expression in CNB and EB, 38/39 (97.4%), 35/39 89.80%) and 36/39 (92.3%) cases showed similar results in both procedures respectively. While 01/39(2.56%), 04/39, (10.20%) and 03/39(7.70%) cases which were negative in CNB proved to be positive in excisional biopsy respectively. So absolute concordance rate between CNB and EB is 97.4% for ER, 89.80% for PR and 92.3% for HER-2/neu expression and discordance rate is 2.56% for ER, 10.20% for PR and 7.70% for HER-2/neu expression.

Various parameters calculated for CNB when EB specimens was regarded as gold standard are as: sensitivity 94.4% for ER, 75.0% for PR and 66.66% for HER-2/neu expression. Whereas specificity and positive predictive values are 100% for all three. (Table 5)

Table 6: Distribution of cases according to histological grade

Grade	Histological types	Total(PCT)
I	08 (IDC), 01 (ILC), 01 (PC)	10(25.64%)
II	17 (IDC)	17(43.58%)
III	11 (IDC), 01 (MC)	12(30.76%)

Out of 39 cases, 10 cases (25.64%) showed histological grade I, 17 cases (43.50%) showed histological grade II and 12 cases (30.70%) showed histological grade III. (Table 6)

Table 7: Comparative evaluation of ER, PR & HER-2/neu overexpression with histological grading

	I	II	III	X^2 test	P value
ER+	9	6	3	10.70	<0.01
ER-	1	11	9		
PR+	9	5	2	13.80	<0.01
PR-	1	12	10		
HER-2/neu +	1	2	6	7.077	<0.01
HER-2/neu -	9	15	06		

Among 10 cases of histological grade I, 09 cases show ER positivity, 09 cases show PR positivity and 01 case shows HER-2/neu expression. In 17 cases of histological grade II, 06 cases show ER positivity 05 cases show PR positivity and 02 case shows HER-2/neu expression & among 12 cases of histological grade III, 03 cases show ER positivity 02 cases show PR positivity and 06 cases show HER-2/neu expression.

The value of (chi square test) x2 at 2df for ER positivity, PR positivity and HER-2/neu expression along with different histological grades were 10.70, 13.80 and 7.077 respectively. Thus a significant inverse association ($p<0.01$) was found between different histological grades of breast carcinoma & ER, PR and HER-2/neu expression. (Table 7)

Table 8: Comparative evaluation of HER-2/neu overexpression with ER and PR status

	ER Positive	ER Negative	PR Positive	PR Negative
HER-2/neu positive (09)	02	07	01	08
HER-2/neu negative (30)	17	13	16	14
Total	19	20	17	22

ER positivity in HER2/neu negative cases (56.6%) was higher than in HER2/neu positive cases (22.2%). Also PR positivity in HER- 2/neu negative cases (53.33%) was higher than in HER-2/neu positive cases (11.11%). (Table 8)

Discussion

Out of 60 cases 39 cases were of malignant breast lesions. These 39 formalin fixed paraffin- embedded tissue sections of invasive carcinoma of breast were screened to assess the HER-2/neu, ER status and PR status by applying immunohistochemical stain using primary monoclonal antibodies (biogenics kit) and its association with well-established parameter like histological grade obtained.

The invasive ductal carcinoma is still commonest carcinoma of breast while fibroadenoma being most common benign lesions of breast. The classification of patients using the system proposed by the NHSBSP help the pathologist to uniformly formulate their reports, which in turn has surely improved the communication between clinicians and pathologists. Moreover, this system of analysis has enabled us to

consider CNB, a reliable and effective methods for diagnosis of breast lesions as in present study our results surpassed the minimum recommended values for various parameters.

The absence of false positives conclusively confirmed the place of CNB not only as a complimentary adjunct but also a substitute of EB in majority of instances. CNB has high specificity and diagnostic accuracy and lower suspicious rate thus helps to determine a definitive treatment to patients with cancer, and in benign results, excision can be performed only at the patient's request. CNB was also found to be highly specific in correctly typing breast lesions and avoids unnecessary surgical management.

Absolute concordance rate between CNB and Excisional biopsy for ER, PR and HER-2/neu expression were found to be very good (>90%) so CNB can be used for analysis of ER, PR & HER-2/neu status in malignant breast lesions. High sensitivity, specificity and positive predictive value of CNB, where EB as gold standard, emphasized that CNB sections can be used for study of ER, PR and HER-2/neu status in malignant breast lesions. The beneficial aspect of above is that the suffering patient would have the earliest possible treatment as the time between the screening by CNB and EB procedure would be saved.

Histological grading of malignant breast lesions showed maximum cases belonged to histological grade II. In study majority of HER-2/neu positive case are of grade-II & III. Both ER and PR positivity was observed mostly in grade-I breast carcinoma. This indicated a significant association between HER-2/neu over expression and histological grade of tumour and an inverse correlation between hormone receptor immunoreactivity and histological grading. The expression of ER and PR was decreased in HER-2/neu positive tumours in comparison to HER-2/neu negative tumours.

Conclusion

There was general agreement that CNB costs less than EB, consumes fewer resources and is preferred by patients. Women are generally satisfied with cosmetic results of CNB. Women who underwent CNB as their first invasive tests to diagnose a breast cancer had an average fewer surgical procedures than women who underwent EB as their first invasive tests.

In our country, FNAC still continues as an initial screening test for both palpable and non-palpable breast lesions. But it has certain pitfalls which increases the number of EB specimen for the diagnosis of breast masses. CNB is less invasive with an increased diagnostic accuracy and can reduce the number of both incisional & excisional biopsies of breast lesions. Due to high concordance results of CNB with EB, it must be used as first screening test for breast lesions. Further CNB also reflects the status of invasion in malignant breast lesion. In view of above two beneficial aspects of CNB, the place of FNAC in triple assessment must be redefined and replaced with CNB.

IHC studies of ER, PR and HER-2/neu expression on CNB were also in excellent concordance with the same study on EB specimen. So on the very first day of screening of a patient diagnosed as breast carcinoma by CNB, the oncologist can calculate the prognosis and accordingly usher the treatment and ultimately the patient may get earliest remedy.

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