



Evaluation of Cytological Profiles of Breast Lesions using FNAC with Special Reference to IAC Yokohama System for Reporting Breast Cytopathology, A Hospital Based Study.

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Abstract

Background: Triple Negative breast cancer (TNBC) constitutes 25-30% of breast cancers in India with aggressive behavior. IAC Yokohama System for reporting Breast cytology standardizes FNAC reporting with Risk of malignancy (ROM) for each category. Concordance between core needle biopsy (CNB) and excision histopathology with immunohistochemistry (IHC) is crucial for early TNBC diagnosis. **Aims & Objectives:** To categorize palpable breast lesions as per Yokohama System, to be calculated ROM and diagnostic accuracy of FNAC against histopathology and assess concordance between CNB and excision for histology and IHC(ER/PR/HER2). **Methods:** Cross-sectional observational study was conducted in the department of pathology at Fakir Mohan Medical college and hospital, Odisha from Jan 2023 to June 2024. After approval of Institutional ethical committee. Written informed consent was obtained. A total of 122 consecutive patients with palpable breast lumps undergoing FNAC were included. **Results:** Out of 122 FNAC, categorization was: C1 Insufficient 10 cases, C2 Benign 45 case (36.9%), C3 Atypical 15 case (12.3%), C4 Suspicious 35 cases (28.7%) and C5 Malignant 17 cases (13.9%). 75 cases were sent for CNB and immunohistochemistry study as per IAC system C1not applicable, C2 15/45 cases diagnosed as fibroadenoma on excised histopathological study as the same report by FNAC but one case turned out to be tubular adenoma with atypia on excision histopathology study. C3 8/15 cases were available for CNB and only 1 case for cellular atypia was found on excisional histopathological study and ROM was 12.5%. C4 Risk of malignancy was 92.9% and on C5 ROM was 100%. Increasing ROM from C2 to C5 was statistically significant (p<0.001, chi-square). **Conclusions:** IAC Yokohama system is highly sensitive and specific for triage of palpable breast lesions. CNB is gold standard and shows perfect concordance with excision for diagnosis and ER/PR status. Routine IHC is essential for therapeutic decision.

Keywords: Yokohama System, FNAC, CNB, TNBC, Risk of Malignancy, ER/PR/HER2.



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INTRODUCTION

Breast cancer is the most common malignancy in woman worldwide and is the leading cause of cancer related mortality among woman. According to GLOBOCAN 2022, breast cancer accounted for 2.3 million new cases and 6.6 lac deaths globally, with incidence rising in low and middle income countries.[1] In India, as per National Cancer Registry Programme 2020, breast cancer has surpassed and now is the most common cancer among women with an age standardized incidence rate of 25.8 per 100,000 women.[2] The majority of patients in India present with palpable breast lumps often at advanced stage, making rapid and accurate diagnosis crucial.[3]

Triple assessment comprising clinical examination, radiology and pathology is considered the gold standard for evaluation of breast lesions, with diagnostic accuracy of >99% when all three modalities are concordant.[4] Fine needle aspiration cytology is a simple, rapid cost effective and minimally invasive first line investigation for palpable breast lesions. However, lack of standardized reporting terminology led to considerable inter-observer variability and confusion among clinicians.[5] To address this, the international academy of cytology (IAC) in collaboration with experts published the IAC Yokohama system for reporting breast cytopathology in 2016 and updated in 2023 at Yokohama, Japan.[6] This system provides a standardized 5-tier categorization: C1-Insufficient, C2 -Benign, C3-Atypical probably benign, C4-Suspicious for malignancy and C5-Malignant with defined risk of Malignancy (ROM) and recommended management for each category.[7]

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The Yokohama system mandates correlation of FNAC categories with histopathology and calculation of ROM, sensitivity, specificity and diagnostic accuracy, CNB provides histological architectures and is considered as gold standard for diagnosis of breast lesions with 96-99% concordance with excision specimens. CNB also provides sufficient tissue for Immunohistochemistry.[8]

Immunohistochemistry for Estrogen RAceptor (ER), Progesterone receptor (PR) and Human Epidermal Growth factor Receptor2 (HER2) is now mandatory for all invasive breast cancer as per ASCO/CAP guidelines 2020, as it provides prognostic information and guides hormone al and targeted therapy.[9] Molecular subtype based on IHC (Luminal A, Luminal B, HER2 enriched, Triple negative) has replaced traditional histological classification for therapeutic decision making.[10] Concordance studies of ER/PR/HER2 status between CNB and excised specimen is essential to ensure that therapy planned on CNB is appropriate and studies show concordance of 88-95% for ER and 85-92%for HER2.[11]

AIMS & OBJECTIVES

To evaluate palpable breast lesions using IAC Yokohama System for reporting breast cytology and to correlate FNAC with CNB, histopathology and immunohistochemistry (ER/PR/HER2). To categorize breast FNAC as per IAC Yokohama System (C1-C5) and calculation of Risk of malignancy (ROM) for each category. To assess diagnostic accuracy of FNAC against histopathology as gold standard and also to assess concordance between CNB and excision histopathology and ER/PR.HER2 status.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the department of pathology at Fakir Mohan Medical college and hospital, Odisha from January 2023 to June 2024. After approval of Institutional ethical committee. Written informed consent was obtained.

A total of 122 consecutive patients with palpable breast lumps undergoing FNAC were included. Of these 75 had CNB and 46 had excision biopsy with IHC available. The cases were categorized as per IAC Yokohama 2016 as C1-insufficient, C2-Benign, C3-Atypical, C4 -Suspicious, C5-Malignant and CNB +immunohistochemistry follow up done for C3, C4, C5 and selectiveC2.

Statistical Analysis

ROM for each category was calculated as proportion of malignant cases on histology. Diagnostic indices (sensitivity, specificity, PPV, NPV, accuracy) were calculated taking C4+C5 as positive C2+C3 as negative. Agreement between FNAC Vs gold standard (CNB+Excision) and CNB IHC Vs excision IHC was assessed by Cohen, s Kappa (k). k0.81-1.00was considered almost perfect. Analysis was done using SPSSv26.0; p<0.05 significant.

RESULTS

Total of 122 cases of primary palpable breast lesions are studied for clinical presentations, associated biological changes and malignant potential using ER, PR and HER2 as immunomarker as per ASCO/CAP 2020. Majority of patients were in mean age 37.2±sd 13. 4 years (range 16-72 years). Mean lump size was 3.1 cm. Most common benign lesion was fibroadenoma followed by fibrocystic diseases. Histopathological follow- up was available in 75 cases among them 29 cases were benign papillomatosis, 28 cases were ductal invasive carcinoma and 18 cases were other malignancy like invasive lobular carcinoma and inflammatory carcinoma. Significant difference was found in all the three groups by age, size, menopausal status, nipple discharge, and axillary lymphadenopathy except in ulceration cases.

Table 1: Clinico-demographic spectrums of breast lesions as diagnosed on Core needle biopsy

Variable	Benign Breast Disease (n=29)	Ductal Invasive Carcinoma(n=28)	Other Malignancies(n=18)	p-value
age	36+2SD	53+3SD	58+5SD	ANOVA P<0.01
Size >5CM	3(2.4%)	18(14.6%)	38(31.2%)	Chi-square P<0.01
Post menopausal	12(9%)	38(31%)	25(20%)	Chi-square P<0.01
Nipple discharge	6(4%)	18(14%)	22(18%)	Chi-square P<0.011
ulceration	3(2%)	7(5%)	8(6%)	Fishers exact test P=0.311(NS)
Axillary LN	5(4%)	48(39%)	40(32%)	Chi-square P<0.001

Table 2: Categorization as per IAC Yokohama System

IAC Category	No. of Cases	Percentage%	Histopathology Available	Malignant on HPE	ROM
C1-insufficient	10	8.19	6	1	16.7
C2-Benign	45	36.9	16	1	6.25
C3-Atypical, probably benign	15	12.3	8	1	12.5
C4-Suspicious	35	28.7	28	26	92.9
C5-Malignancy	17	13.9	17	17	100%
TOTAL	122	100	75	46	--

Out of 122 FNAC ,categorization was: C1 Insufficient 10 cases, C2 Benign 45 case (36.9%), C3 Atypical 15 case (12.3%), C4 Suspicious 35 cases (22.9%) and C5 Malignant 17 cases (13.9%).75 cases were sent for CNB and immunohistochemistry study as per IAC system C1not applicable, C2 15/45 cases diagnosed as fibroadenoma on excised histopathological study as the same report by FNAC but one case turned out to be tubular adenoma with atypia on excision histopathology study.C3 8/15 cases were available for CNB and only 1 case for cellular atypia was found on excisional histopathological study and ROM was 12.5%. C4 Risk of malignancy was 92.9% and on C5 ROM was 100%. Increasing ROM from C2 to C5 was statistically significant ($p<0.001$, chi-square).

Table 3: Diagnostic performance of FNAC

	HPE Malignant (46)	HPE Benign (29)	Total
FNAC C4+C5(test positive)	TP=43 (26+17)	FP=2 (2+0)	45
FNAC C2+C3(test negative)	FN=2 (1+1)	TN=22 (15+7)	24
C1 excluded	1 Malig/5 Benign		6
Total with HPE	45(exclC1)/46	24(exclC1)/29	69/75

Table 4: Diagnostic performance and role of CNB for concordance with excision immunohistochemistry

	FNAC(n=122)	CNB(n=75)	Histopathology + IHC(n=46)
Sensitivity	95.56%	100% (reference)	NA
specificity	91.67%	100% (reference)	NA
PPV	95.56%	--	ER+=48% PR+=48% HER2+=18%
NPV	91.67%		TNBC=34%
Accuracy	94.20%	--	
Cohens Kappa	0.87	--	Concordance CNB Vs excision for ER/PR = 100%, Kappa=1.0

Table 5: 2*2 table for Kappa(n=69)

	CNB+IHC B5(malignant)	CNB (benign)	Total
FNAC C4+C5	43	2	45
FNAC C2+C3	2	22	24
Total	45	24	69

Diagnostic indices were true positive:43, true negative: 22, false positive: 2, false negative: 2, Sensitivity: 95.56% (95% CI:84.8-99.4%), specificity: 91.67% (95% CI: 73.0-98.9%), PPV: 95.56%, NPV: 91.67%, Diagnostic accuracy: 94.20% and Cohen, s Kappa(k): 0.87(95% CI: 0.75-0.99) indicating almost perfect agreement $p<0.001$.

CNB was performed in 75 cases. All 46 cases where both CNB and excision were available showed 100% concordance for histopathology type and guide. IHC was available in 46 malignant cases and subtyping as ER Positive:22/46(47.8%), PR Positive:22/46(47.8%), HER2 Positive:8/46(17.4%) and triple negative:14/46(30.4%). Among 46 paired CNB - excision samples, concordance for ER was 100%, PR was 100% and HER2 was 93.5% ($k=0.86$, almost perfect). Weighed kappa across 5 tier vs 2-tier was 0.81(95%CI:0.69-0.93, $p<0.001$) indicating good agreement even when grey zone categories(c3) were included.

DISCUSSION

In our study c2(benign) was the commonest category followed by c5(malignant)27.0%(33/122).This distribution is concordant with studies by Montezuma et al.^[12] and Kamatar et al (c2-56%,c5-24%).^[13] The slightly higher risk of malignancy(ROM) in C2 in our study(6.25%) is due to two false negative cases .Similar higher ROM for C2 (7.1%) was

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reported by Wong et al.^[14] When C1 was excluded and C2+C3 were taken as negative test and C4+C5 as positive test(as recommended by Yokohama), the sensitivity ,specificity, PPV,NPV and diagnostic accuracy of FNAC in our study were 95.56%,91.67%,and 94.20% respectively. This is comparable to meta-analysis of FNAC by Rocha et al.^[15] The subtyping after excisional immunohistochemistry by our study were ER+ 48%, PR+ 48% HER2+ 18% and TNBC 30% which were similar to study by Ghosh et al.^[16] The agreement between Yokohama categories (C2+C3 Vs C4+C5) and final gold standard (CNB+IHC B2 Vs B5) was evaluated. The observed agreement was 94.2% with Cohen s kappa =0.87(p<0.001,95% CI:0.75-0.99) as similar agreement by De Rose et al.^[17]

Table 5: Comparison of other studies with our study's

Studies	distribution as Yokohama	ROM	Performance of FNAC	Role of CNB	IHC and molecular Type	Concordance	Agreement analysis
Montezuma et al. ^[12]	C1 5.7% C2 73.3% C4 2% c5 5.5%	C1 4.8% c2 1.4% c3 13% c4 97.1% c5 100%	Sens 98.3% spec 54.8% PPV 100% Acc 68.2%	CNB gold standard	Not assessed	Not assessed	Not reported
Kamatar et al. ^[13]	C1 5% c2 71% c3 1% c4 2% c5 21%	C1 0% c2 4% c3 66% c4 83% c5 99%	Sens 94.59% spec 98.9% acc 96.97%	Histology gold standard	Not assessed	Not assessed	Not reported
Wong et al. ^[14]	C1 11% c2 72% c3 4.3% c4 2.2% c5 10%	C1 2.6% c2 1.7% c3 15.7% c4 84.6% c5 99.5%	Sens 98.9% spec 62.1% acc 80.2%	CNB as gold std	Not assessed	Not assessed	Not reported
Rocha et al. ^[15]	Meta 46 studies	C2 1-3%, c3 17-23% c4 79-92% c5 99-100%	Pooled sens 92.7% spec 94.8%	CNB higher accuracy than FNAC	Not primary focus	FNAC vs CNB acc93.2%	Not reported
Ghosh et al. ^[16]	NA	NA	NA	NA	ER+51% PR+40% ER/PR both+30% her2+10-20%, TNBC 25-30%	ER/PR low in Indian (32-51%)	Not reported
De Rose et al. ^[17]	C1 19.2% c2 36.9% c3 10.8% c4 4.7% c5 28.4%	C1 49.6% c2 4.9% c3 20.7% c4 78.7% c5 98.8%	Sens 95.56% spec 91.67% acc 94.20%	Histology gold std	Not assessed	Not assessed	Kappa 0.84-0.91
Our study	C1 1.6% c2 41.8% c3 6.5% c4 22.9% c5 27%	C1 NA c2 6.25% c3 12.5% c4 92.9% c5 100%	Sens 95.56% spec 91.67% acc 94.20%	CNB=gold 100% concordance	Er+48% pr+48% her2+ 18% TNBC 30%	CNB vs excision 100% kappa 1.0	Kappa 0.87, p<0.001

CONCLUSION

IAC Yokohama system is highly sensitive and specific for triage of palpable breast lesions. CNB is gold standard and shows perfect concordance with excision for diagnosis and ER/PR status. Routine IHC is essential for therapeutic decision. Limitations of study were single center study with 122 cases where 46 excised masses, c1 cases were less with follow-up data and HER2 equivocal cases were not confirmed by FISH due to resource constraints.

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