

Breast fine-needle aspiration cytology reporting using international academy of cytology Yokohama system: A single institution experience



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ABSTRACT

Background: Worldwide breast malignancy is the major cause for mortality among women. Screening and early detection are crucial. Grey zones of uncertainty in cytomorphological differentiation of benign from malignant lesions can be overcome by Yokohama system of classification. **Aims and Objectives:** The objectives of this study are as follows: (1) To categorize Breast fine needle aspiration cytology (FNAC) samples according to the international academy of cytology (IAC) Yokohama system. (2) To assess the diagnostic accuracy, sensitivity, specificity, and risk of malignancy (ROM) for each category. **Materials and Methods:** A retrospective study of 144 breast FNAC cases with histopathological diagnosis was done based on Yokohama System from January 2018 to December 2020. ROM in each category was calculated. The study results were analyzed for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) considering histological diagnosis as the gold standard. **Results:** Recategorization of 144 cases with histopathological diagnosis was done according to Yokohama system as insufficient material, benign, atypical, suspicious for malignancy, and malignant. The respective ROM for each category was, 7.6% for Category-1 (Insufficient), 15.26% for Category-2 (Benign), 65.38% for Category-3 (Atypical), 83.33% for Category-4 (Suspicious), and 99.18% for Category-5 (Malignant). Considering malignant cases as positive, sensitivity – 86.75%, specificity – 97.32%, PPV – 99.19%, NPV – 66.06%, and accuracy of 88.96% were deduced. **Conclusion:** Incorporation of IAC Yokohama system to categorize breast cytopathology using uniform terminologies provides diagnostic clarity, consistency, and accuracy in reporting, which in turn helps the clinician to predict the ROM and patient outcome.

Key words: Breast; Fine-needle aspiration cytology; Yokohama system

INTRODUCTION

Worldwide breast cancer is the most common malignancy in women. The global incidence is about 2.3 million cases each year, and in India, it is 1,78,361/year.¹ It is the leading cause of mortality in females especially in developing countries. Breast cancer has overtaken cervical cancer in India with the incidence rate being 26/100,000 women population and a mortality rate of 13/100,000 women population, thus emphasizing the crucial role of screening

and early detection of breast malignancies and in lowering the mortality rate.²⁻⁴

With the advent of triple testing for breast malignancies which includes clinical examination, mammography, and fine-needle aspiration cytology (FNAC); cytomorphological diagnosis plays a pivotal role in assessment of any suspicious lesion of breast.⁵ FNAC is a simple, non-invasive, economically feasible, and rapid technique, which facilitates early detection of breast malignancies by

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categorizing a breast lump into either benign or malignant lesion.⁶

Even though histomorphology remains the gold standard, cytohistopathological correlation will be of great significance for the final diagnosis as it will increase the precision.⁶ However, cytopathologists encounter difficulties in day-to-day practice, due to overlap of cytomorphological features of breast lesions to a significant extent. Differentiating benign from malignant lesions may not be possible in certain cases, for example, (i) benign from borderline phyllodes, (ii) usual ductal hyperplasia from intraductal papilloma, (iii) cellular fibroadenoma from low-grade phyllodes, and (iv) lobular carcinoma *in situ* from invasive lobular carcinoma.^{5,7} These grey zone areas of uncertainty turn out to be a diagnostic challenge. To overcome this drawback and to create a degree of uniformity in reporting system, the international academy of cytology (IAC) Yokohama System for Reporting Breast Cytopathology has proposed a classification of five categories in 2016, which will unmask the diagnostic dilemma and bridge the communication gap between the clinician and pathologist and strive toward better patient care.^{5,8} The categories are as follows: Category 1 – Insufficient material: Defined as smears which are sparsely cellular or poorly smeared or fixed to allow a cytomorphological diagnosis. It is advised that an adequate smear shows the presence of seven tissue fragments with each consisting of 20 or more epithelial cells will allow assessment of the architecture and the presence or absence of myoepithelial cells should be a measure of adequacy. If there are any atypical epithelial features or necrosis, even if there are fewer than seven tissue fragments, the case should be reported as atypical. The reason for the categorization as insufficient/inadequate should always be stated in the report.⁷ Category 2 – Benign: Lesions have unequivocally benign cytological features, which may or may not be diagnostic of a specific benign lesion. The key cytological features of benign lesions include a pattern of predominantly large cohesive three-dimensional tissue fragments and flat mono-layered sheets consisting of evenly spaced, ductal epithelial cells with myoepithelial cells creating a “bimodal” pattern, as well as, “bare bipolar nuclei” representing stripped myoepithelial nuclei, in the background.⁷ Category 3 Atypical, probably Benign: It is defined as the presence of cytological features seen predominantly in benign processes or lesions, but with the addition of some features that are uncommon in benign lesions and which may be seen in malignant lesions. The specific cytological features that are considered atypical, such as high cellularity, increased dispersal of single intact cells, enlargement and pleomorphism of nuclei, presence of necrosis or mucin, and complex micropapillary or cribriform architecture of epithelial tissue fragments, should always be stated. The report, if possible, should include the differential

diagnosis.⁷ Category 4 – Suspicious for malignancy, probably *in situ* or invasive carcinoma: It is defined as the presence of some cytomorphological features, which are usually found in malignant lesions, but with insufficient malignant features, either in number or quality, to make a definitive diagnosis of malignancy. The type of malignancy suspected should be stated whenever possible. The cytological features of proliferative lesions and low-grade or *in situ* carcinomas overlap, and great care has to be taken in assessing smear patterns and nuclear atypia.⁷ and Category 5 – Malignant: It is an unequivocal statement that the material is malignant, and the type of malignancy identified should be stated whenever possible. The key cytological findings include high cellularity, prominent dispersal of single cells, crowded tissue fragments with overlapping nuclei, and most importantly, nuclear enlargement, anisonucleosis, pleomorphism of the nuclear margin, size and chromatin, hyperchromasia, and prominent nucleoli.^{7,8}

Aims and objectives

The objectives of this study are as follows:

1. To categorize the Breast FNAC samples according to the IAC Yokohama reporting system
2. To assess the diagnostic accuracy, sensitivity, and specificity of breast FNAC and calculate the risk of malignancy (ROM) for each category.

MATERIALS AND METHODS

This is a retrospective study of patients who underwent breast FNAC between January 2018 and December 2020 at our tertiary care center. Only those cases with histopathological reports were included in the study. Cytological findings were reclassified according to the newly proposed IAC Yokohama reporting system. The ROM for each category was determined. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were evaluated. The histopathological report was considered as the gold standard. The ROM was calculated for each category using the formula, number of confirmed malignant cases to the total number of cases in the diagnostic category.

Inclusion criteria

Both ultrasound guided and direct breast FNAC of all age groups and both sexes with histopathological reports were included in the study.

Exclusion criteria

Inflammatory conditions of breast and lymph node biopsies alone and previously treated or recurrence/repeat biopsies were excluded from the study.

For statistical analysis, all forms of malignancy were included under Category 5 such as all invasive carcinomas, DCIS, borderline and malignant Phyllodes tumors, sarcomas, and lymphomas were considered as malignant and all other lesions (including benign Phyllodes tumors, atypical ductal hyperplasia, papilloma, fibroadenoma, fibrocystic change, and acute/chronic inflammatory disease) were considered as benign.

The study results were analyzed using Microsoft Excel 2007 and sensitivity, specificity, PPV, NPV, and accuracy ratios were calculated using the MedCalc diagnostic test evaluation calculator, keeping histologic diagnosis as the gold standard.

The accuracy of breast FNAC in diagnosing malignancy was calculated for the following diagnostic scenarios: Considering only the benign category as non-malignant on cytology and the atypical, suspicious of malignancy and malignant categories is a malignant report.

RESULTS

A total of 187 patients were subjected to breast FNACs, of which histopathological correlation was obtained in 144 cases (77%). The age ranged from 17 to 75 years with mean age of 43 years. Male to female ratio was 1:59 (males=3, females=141). Among the 144 cases, ultrasound-guided FNACs were 37, and direct FNACs were 107. Left-sided lesions were 63 right-sided lesions were 76 and bilateral were 5.

Re-categorization of 144 cases with histopathological diagnosis was done according to Yokohama system as insufficient material, benign, atypical, suspicious for malignancy, and Malignant (Figure 1).

The respective ROM for each category was 11% for Category-1 (Insufficient), 3% for Category-2 (Benign), 31% for Category-3 (Atypical), 91% for Category-4 (Suspicious), and 100% for Category-5 (Malignant) (Table 1).

The performance indicators in each category were as shown in Table 2. The overall performance indicators were sensitivity – 86%, specificity – 98.7%, PPV – 98%, NPV – 90.6%, and accuracy of 93.3%.

DISCUSSION

With the rapid increase in the incidence of mortality and morbidity among the female population due to breast malignancy, the role of triple test which consists of thorough clinical examination, mammography, and FNAC

is vital in definitive evaluation and assessment of breast lesions.⁹ IAC Yokohama system helps to stratify breast lesions into five categories and based on ROM, management algorithm for each category can be cumulated.¹⁰ The study done by Montezuma et al., was the first to categorize breast FNAC cytology samples and evaluate the patient outcome incorporating IAC reporting system.⁴

FNAC of breast lesions has been the primary low-cost investigation which is highly sensitive and specific diagnostic tool, especially in Indian scenario. There is limited data available in the literature, especially in the Indian population¹⁰ regarding the application of the IAC Yokohama System for Reporting Breast FNAC. Our study is unique as we have not only classified the breast FNAC cases based on Yokohama classification, we have correlated FNAC diagnosis with histopathological diagnosis and assessed sensitivity, specificity, PPV, NPV, and accuracy of FNAC in diagnosing the cases in each category. Breast lesions were stratified according to ROM to formulate a management algorithm protocol. This emphasizes the need for more such studies in various regions of India to get proper insight and to standardize reporting pattern of breast cytology.

There is an increasing awareness among clinicians regarding the application of the cytological technique of FNAC aided with ultrasonographic localization of lesion in preoperative assessment, application of ancillary techniques like immunocytochemistry for estrogen receptor, progesterone receptor, and proliferation index (Ki67), along with molecular genetic techniques like fluorescence *in situ* hybridization or chromogen ISH and polymerase chain reaction and DNA pattern analysis with satisfactory results.^{11,12}

Good quality FNAC is replacing core needle breast biopsies due to better yield of cancer cells than core needle biopsies, thereby avoiding the contamination of stromal component encountered in core needle biopsies.¹²

Five categories are defined by IAC Yokohama System for reporting breast cytology, each category as a precise descriptive term, a definition, a ROM, and a management algorithm.^{7,8,13} This study stratifies the breast lesions into five categories and ROM associated with each category.

In the studies done by Montezuma et al., and Wong et al., ROM for Category 2 and 3 was low in comparison to the present study (Table 3), due to incorporation of rapid on-site evaluation (ROSE), which decreased the percentage of insufficient category from 17.1% without ROSE to 4% with ROSE.^{4,15} In study done by Kamatar et al., Wai et al., ROM for Category 1 is low. However, in the present study, the ROM for Category 1 was higher in comparison for other studies as one ultrasound-guided

Table 1: Correlation of Yokohama category with corresponding histopathology diagnosis (HPE) and ROM

Category	Yokohama	FNAC (n) (%)	HPE-Benign	HPE-Malignant	ROM (%)
Category 1	Insufficient	9 (06)	8	1	11
Category 2	Benign	66 (46)	64	2	3
Category 3	Atypical	19 (13)	13	6	31
Category 4	Suspicious	11 (08)	1	10	91
Category 5	Malignant	39 (27)	0	39	100
		144 (100)	86 (60%)	58 (40%)	

ROM: Risk of malignancy, FNAC: Fine-needle aspiration cytology

Table 2: Sensitivity, specificity, PPV, NPV, and accuracy rate of each category

Category	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Category 1	1.72	91.11	11.11	58.99	56.08
Category 2	3.45	25.58	3.03	28.21	16.67
Category 3	10.34	84.88	31.58	58.40	54.86
Category 4	17.24	98.84	90.9	63.9	65.97
Category 5	67.24	100	100	81.9	86.81

PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Comparison of risk of malignancy (ROM) with other studies

Category	Wai et al. 2013 ¹⁴	Montezuma et al. 2019 ⁴	Kamatar et al. 2019 ⁵ (%)	Wong et al. 2019 ¹⁵ (%)	Hoda and Brachtel, 2019 ¹⁶	Nargund et al. 2021 ⁹ (%)	Present study (%)
Category 1	4.8	2.6–4.8	0	2.6	30.3	7.6	11
Category 2	1.4	1.4–2.3	4	1.7	4.7	15.26	3
Category 3	13	13–15.7	66	15.7	51.5	65.38	31
Category 4	97.1	84.6–97.1	83	84.6	85.4–98.7	83.33	91
Category 5	100	99–100	99	99.5	98.7	99.18	100

FNAC case was false negatively reported as insufficient but later turned out to be malignant on histopathology, probably due to sampling error caused by limited training of radiologist in performing FNAC. This can also happen if FNAC material is obtained without proper imaging guidance and in defective procedure of making good-quality smears, and working alone without the availability of ROSE performed by a cytopathologist.⁴ This stresses the importance that breast FNAC requires specific training and ongoing experience which is again a part of Yokohama system which defines the best practice guidelines for the use of FNAC in diagnosing breast lesions.^{7,9}

A meta-analysis done by Hoda and Brachtel, drawn from 27 studies through a PubMed database¹⁶ and studies done by Kamatar et al., and Nargund et al., the ROM obtained for atypical category was 51.5%, 66%, and 65.38%, respectively,^{5,9} which is higher than other studies and is a similar observation in the present study. It was concluded in several studies that each diagnostic category of the new IAC Yokohama System carries an implied ROM, which increases from Category 2 to Category 5 which is similar observation in other studies and the present study.^{4,8,13,14}

The sensitivity (67.24%), specificity (100%), PPV (100%), and NPV (81.9%) were higher for the malignant category with an accuracy of 86.81% in the present study which was similar to studies done by Wong et al., where sensitivity for malignant lesions was 85.3% and specificity of 100%, respectively¹⁵ and Nargund et al., where sensitivity for malignant lesion was 86.75% and specificity of 97.32%, respectively (Table 4).⁹

Limitations of the study

Various studies in the literature have incorporated different methodologies, statistical calculations, and categories that do not exactly align with the categories in the IAC System. It is found that the current ROM needs to be more refined by future research, similar to the modifications of the Bethesda System for Reporting Thyroid Cytology.⁷ All cases with insufficient material should undergo repeat FNAC as a routine protocol, if the index for clinical and radiological suspicion of malignancy is high.⁹

CONCLUSION

The performance indicators, namely, high sensitivity and specificity in each category suggest excellent accuracy for breast FNAC using IAC Yokohama System. FNAC serves

Table 4: Comparison of performance indicators of breast FNAC with other studies

Statistical parameters	Montezuma et al. ⁴ (%)	Moschetta et al. ¹⁷ (%)	Kamatar et al. ⁵ (%)	Nargund et al. ⁹ (%)	Present study (%)
Sensitivity	97.56	97	94.59	95.9	85.9
Specificity	100	94	98.9	97.89	98.72
Positive predictive value	100	91	98.59	96.79	98
Negative predictive value	98.62	98	95.74	97.64	90.6
Diagnostic accuracy	99.11	95	96.97	98.57	93.3

FNAC: Fine-needle aspiration cytology

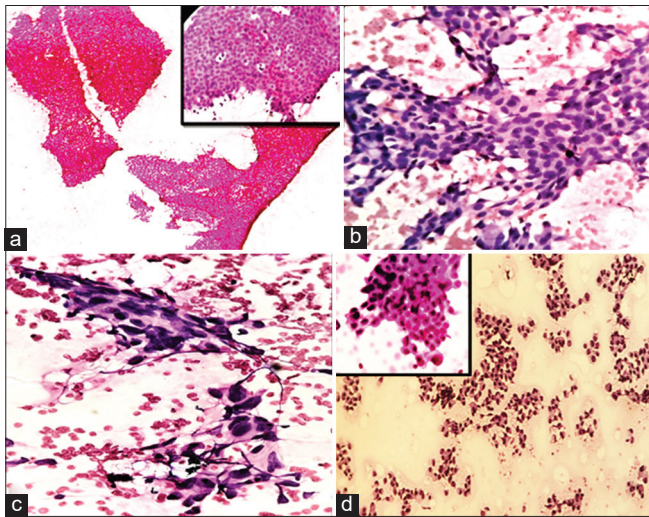


Figure 1: (a) Category 2: Benign-Fibroadenoma (H and E, $\times 10$) (Inset-H and E, $\times 40$). (b) Category 3: Atypical (H and E, $\times 40$). (c) Category 4: Suspicious of malignancy (H and E, $\times 40$). (d) Category 5: Malignant-ductal carcinoma (H and E, $\times 10$) (inset-H and E, $\times 40$)

as an effective diagnostic tool and requires specific training and ongoing experience which will aid in early accurate screening and triage of breast lesions.^{9,17}

The five diagnostic categories of the IAC Yokohama System represent a simple standardized reporting system that allows greater diagnostic clarity, consistency, and accuracy of FNAC. The Incorporation of the IAC Yokohama system for Reporting Breast Cytopathology using uniform terminologies will serve as a common language of communication; providing contemporary global guidelines which will simplify clinical audits worldwide enable better interchange between different hospitals and institutes facilitating reproducibility of reports across institutions. This means of communication will bridge the gap between the clinician and pathologist, ultimately leading to effective stratification of breast lesions, prediction of ROM with clear benefits for patient diagnosis, management, and better patient care.¹⁸

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Authors Contribution:

SGM- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **BTG**- Manuscript preparation, editing, and manuscript revision; design of study, statistical analysis and interpretation; literature survey and preparation of figures; **ML**- Clinical protocol, manuscript preparation, editing, and manuscript revision, statistical analysis, and interpretation; **SPK**- Manuscript revision.

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