Evaluating The Accuracy Of Fine Needle Aspiration Cytology Of Breast Lesion Using International Academy Of Cytology Yokohama System: A Study In Eastern Nepal

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ABSTRACT

Introduction: Breast Carcinoma is the most common cancer in females worldwide. In developing countries, it is the most common cause of cancer-related deaths in women. The IAC Yokohama breast FNAB reporting system was developed as a multidisciplinary approach to have a standardized and structured report, for improvement in interpretation of breast cytology.

Objectives: This study aims to classify Fine needle aspiration cytology of breast lesion according to the IAC Yokohama system and assess diagnostic accuracy of different categories.

Methodology: This was a hospital based prospective cross-sectional study conducted in the Department of Pathology, Birat Medical College Teaching Hospital from August 2022 to May 2023.

All patient with Breast lesions who underwent FNAB were included in the study. FNAB were categorized using IAC Yokohama reporting system. Considering histopathology as a final diagnosis sensitivity, specificity, PPV, NPV, Diagnostic accuracy and Risk of Malignancy were calculated.

Results: One hundred and fifty-six patients underwent FNAB during the study period and 124 patients had histopathological reports available. Frequency of FNAB using Yokohama System were: Inadequate -1.9%, Benign- 59%, Atypical 14.7%, Suspicious- 11.5%, Malignant- 12.8% respectively.

The Risk of Malignancy for each category were 33%, 1.51%, 22.22%, 94.11% and 100% respectively. Maximum sensitivity (97.56%) and NPV (98.48%) was achieved when considering Atypical, Suspicious for Malignancy and Malignant category as Positive. Whereas highest specificity (97.56%) and PPV (100%) was achieved when considering only the Malignant category as Positive.

Conclusion: The IAC Yokohama System is a standard tool for diagnosing Breast FNAB with greater reproducibility and maximum diagnostic accuracy.

INTRODUCTION

Breast Carcinoma is the most common cancer in females worldwide. In developing countries, it is the most common cause of cancer-related deaths in women. Whereas, in developed nations, it is the second common cause of cancer-related deaths subsequent to lung cancer. In the context of Nepal, GLOBOCAN 2020 suggested breast carcinoma as the second most common cancer in female of all ages (17.1%).

Fine needle aspiration biopsy (FNAB) cytology is recognized as a well- validated, rapid and cost-effective procedure in evaluating benign and malignant breast lesions especially in developing nations with limited resources. It is a minimally invasive procedure and is accepted as a valuable tool for diagnosis and management.
FNAB has sensitivity of 90-95% for breast cancer diagnosis and positive predictive value (PPV) approaching 100%. It has low false negative and false positive rates.\(^4\)

The Fine Needle Aspiration cytology findings should be interpreted along with clinical and radiological findings as a part of “triple test.” This triple test assessment, showed that the sensitivity and specificity of FNAC is comparable to core needle biopsy.\(^5\)

The IAC Yokohama Breast FNAC Reporting system has been developed by a group of expert cytopathologists. They were assisted by surgeons, oncologists, and radiologists.\(^3\) The IAC Yokohama breast FNAB reporting system was developed as a multidisciplinary approach. The purpose of this reporting system is to have a standardized and structured report, for improvement in interpretation of breast cytology.\(^6\)

IAC Yokohama utilize five-tier system with diagnostic categories as:

- **C1:** Insufficient/Inadequate
- **C2:** Benign
- **C3:** Atypical
- **C4:** Suspicious of Malignancy
- **C5:** Malignant

These five categories in IAC Yokohama reporting system allow to stratify risk of malignancy (ROM) and also suggest management guidelines to improve diagnostic performance and reproducibility. Further it improves communication between the cytopathologist and clinician by linking reporting system with management perspectives.\(^3\)

This study aims to classify Fine needle aspiration cytology of breast lesion according to the IAC Yokohama system and assess diagnostic accuracy of different categories.

**METHODOLOGY**

This was a hospital based prospective cross-sectional study conducted among patients who underwent FNAC and histopathology for their breast lesions at Birat Medical College Teaching Hospital from August 2022 to May 2023. The study was approved by the Institutional Review Committee (Ref: IRC-PA-216/2078-79).

The sample size for this cross-sectional study was calculated using the formula:

\[
N = \frac{Z^2pq}{d^2},
\]

Where \(N\) =Sample size, \(Z\) = 1.96 (95% confidence interval), \(p=\)prevalence, \(q=1-p\) and \(d=\) 10% of prevalence.

In the study done by Ahuja et al.\(^7\) the sensitivity of malignant case was 79.2%, considering this article as reference, the sample size comes to \(\approx 106\).

Considering 10% as the dropout, the final sample size comes \(106 + 10\% \times 106 = 106 + 10.6 = 117\) However, we enrolled 156 patients as we included all the patients during the study period. The inclusion criteria was patients who underwent FNAC of their breast lesions. Patients who were male and those who refused to participate in the study were excluded.

Under aseptic condition FNAB was done using 24–26-gauge needle attached to 10 ml syringe. Ultrasound guided FNAB was done in those patients where swelling was not palpable or in those patients with inadequate material on first attempt.

The aspirated material was immediately transferred into the glass slide and were air dried and fixed in ethyl alcohol and stained with Giemsa stain and Papanicolaou stain respectively. The slides were evaluated by 2 pathologists.

FNAB was reported using IAC Yokohama system and were categorized in five categories as:

- **C1:** Insufficient/Inadequate
- **C2:** Benign
- **C3:** Atypical
- **C4:** Suspicious of Malignancy
- **C5:** Malignant

Histopathological examinations were done for only those specimens which were available. The specimen was processed, microtomed and subsequently stained with Hematoxylin and Eosin stain. Histopathological features were evaluated by 2 pathologists.

Data was entered in the MS Excel and analyzed by IBM SPSS version 27. The risk of malignancy (ROM) was calculated for each category as the number of malignant cases confirmed histologically/total number of cases in the diagnostic category. The cases in the insufficient category were excluded from further statistical analysis, as they could not be included in either negative or positive for malignancy. Using the histological diagnosis as the gold standard, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and risk of malignancy were calculated using the following equations:

- **Sensitivity** = True positive/(True positive + False negative)
- **Specificity** = True negative/(True negative + False positive)
- **PPV** = True positive/(True positive + False positive)
- **NPV** = True negative/(True negative + False negative)
- **Diagnostic accuracy** = (True positive + True negative)/All analyzed cases

**RESULTS**

One hundred fifty-eight patients underwent FNAB during the study period, 2 were excluded and 124 patients had histopathological reports available (Figure 1). The mean age of the patients was 35.72±13.48 years. The lesions were on the right side in 76 cases (48.71%), left side in 69 cases (44.23%) and bilateral in 11 cases (7.05%) respectively.

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Frequency of FNAB using Yokohama System were: Inadequate – 3 cases (1.9%), Benign- 92 cases (59%), Atypical – 23 cases (14.7%), Suspicious- 18 cases (11.5%), Malignant- 20 cases (12.8%) respectively. The Risk of Malignancy for each category were 33%, 1.51%, 22.22%, 94.11% and 100% respectively.

Histopathological examination was available in 124 cases. The Histopathological diagnosis in different cytological categories were evaluated and summarized with cyto-histological correlation in Table 1. Distribution of IAC Yokohama System categories with cyto-histological correlation and Risk of Malignancy. (Table 1)

Table 1: Distribution of IAC Yokohama System categories with cyto-histological correlation and ROM.

<table>
<thead>
<tr>
<th>Insufficient</th>
<th>Benign</th>
<th>Atypical</th>
<th>Suspicious</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrocystic Changes-2</td>
<td>Fibrocystic changes- 34</td>
<td>Benign Phyllodes-7</td>
<td>Atypical Ductal Hyperplasia-1</td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma-16</td>
<td>Atypical Ductal Hyperplasia-4</td>
<td>Usual Ductal Hyperplasia-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual Ductal Hyperplasia-7</td>
<td>Fibrocystic changes -1</td>
<td>Tubular Adenoma-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactational Changes-5</td>
<td>Granulomatous Mastitis-3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Histological Malignant Diagnosis

<table>
<thead>
<tr>
<th>Invasive Ductal Carcinoma-1</th>
<th>Ductal Carcinoma Insitu-3</th>
<th>Invasive Carcinoma NOS-12</th>
<th>Invasive Carcinoma NOS-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal Carcinoma Insitu-1</td>
<td>Invasive Carcinoma NOS-1</td>
<td>Apocrine Carcinoma-1</td>
<td>Ductal Carcinoma Insitu-3</td>
</tr>
<tr>
<td>Invasive Carcinoma NOS-1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk of Malignancy

33.33% 1.51% 22.22% 94.11% 100%

The results of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of FNAB Yokohama system were as below (Table 2)
Table 2: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of FNAB Yokohama system

<table>
<thead>
<tr>
<th>Category</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>48.78%</td>
<td>100%</td>
<td>100%</td>
<td>79.20%</td>
<td>82.64%</td>
</tr>
<tr>
<td>B</td>
<td>87.80%</td>
<td>98.75%</td>
<td>97.29%</td>
<td>94.04%</td>
<td>95.04%</td>
</tr>
<tr>
<td>C</td>
<td>97.56%</td>
<td>81.25%</td>
<td>72.72%</td>
<td>98.48%</td>
<td>86.77%</td>
</tr>
</tbody>
</table>

Category A: included malignant lesions as positive.
Category B: included atypical, suspicious and malignant as positive.
Category C: included atypical, suspicious, and malignant as positive.

Maximum sensitivity (97.56%) and NPV (98.48%) was achieved when considering Atypical, Suspicious for Malignancy and Malignant category as Positive. Whereas highest specificity (100%) and PPV (100%) was achieved when considering only Malignant category as Positive.

The highest Diagnostic Accuracy (95.04%) was achieved when Suspicious and Malignant categories were considered as Positive.

DISCUSSION

Breast Carcinoma is the most common cancer in females worldwide. In developing countries, it is the most common cause of cancer-related deaths in women. Fine needle aspiration biopsy (FNAB) cytology is recognized as a well-validated, rapid and cost-effective procedure in evaluating benign and malignant breast lesions especially in developing nations with limited resources. The FNAB has sensitivity of 90-95% for breast cancer diagnosis and positive predictive value (PPV) approaching 100%. It has low false negative and false positive rates.

The IAC Yokohama breast FNAB reporting system was developed as a multidisciplinary approach. The purpose of this reporting system is to have a standardized and structured report, for improvement in interpretation of breast cytology.

Our all patients were females and the mean age was 35.72±13.48 years (range 15-86 years). The lesions were bilateral in 7.05% of cases. This is comparable to the study of Ahuja et al. where age of the patients ranged from 15-79 years and lesions were bilateral in 3.2%. The age range of our patients was comparable to the patients of the study of Sreevidyalatha et al ranging from 17 years to 75 years. Similarly, the lesions were bilateral in 10.47% in the study of Chauhan and colleagues.

We have compared the distribution of FNAB using Yokohama System with other studies. (Table 3)

Table 3: Comparison of distribution of FNAB using Yokohama System with other studies.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Wong et al.</th>
<th>Montezuma et al.</th>
<th>Kamatar et al.</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate</td>
<td>301 (11%)</td>
<td>209 (5.77%)</td>
<td>22 (5%)</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Benign</td>
<td>1937 (72%)</td>
<td>2660 (73.38%)</td>
<td>332 (71%)</td>
<td>92 (59%)</td>
</tr>
<tr>
<td>Suspicious</td>
<td>117 (4.3%)</td>
<td>498 (13.74%)</td>
<td>7 (1%)</td>
<td>23 (14.7%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>59 (2.2%)</td>
<td>57 (1.57%)</td>
<td>8 (2%)</td>
<td>18 (11.5%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>278 (10%)</td>
<td>201 (5.54%)</td>
<td>101 (21%)</td>
<td>20 (12.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>2696</td>
<td>3625</td>
<td>470</td>
<td>156</td>
</tr>
</tbody>
</table>

The number of inadequate samples in our study was less than others. Our samples were ultrasound guided facilitating more targeted aspiration reducing number of inadequate samples.

We have calculated the risk of malignancy for each category and compared it with other studies. (Table 4)

Table 4: Comparison of Risk of Malignancy for each category with other studies.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Montezuma et al.</th>
<th>Kamatar et al.</th>
<th>Aithmia et al.</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate</td>
<td>4.8%</td>
<td>0%</td>
<td>0%</td>
<td>33.33%</td>
</tr>
<tr>
<td>Benign</td>
<td>1.4%</td>
<td>4%</td>
<td>2.27%</td>
<td>1.51%</td>
</tr>
<tr>
<td>Atypical</td>
<td>13%</td>
<td>66%</td>
<td>50%</td>
<td>22.22%</td>
</tr>
<tr>
<td>Suspicious</td>
<td>97.1%</td>
<td>83%</td>
<td>50%</td>
<td>94.11%</td>
</tr>
<tr>
<td>Malignant</td>
<td>100%</td>
<td>99%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
The risk of malignancy for all categories were also comparable with the study of Dixit and team and Apuroopa and colleagues as well as original publication of Yokohama System except for inadequate category in which the Risk of Malignancy was higher (33%) than others.\textsuperscript{17,18} This can be attributed to a smaller number of samples in the category.

In the current study, maximum sensitivity (97.56%) and NPV (98.48%) was achieved when considering Atypical, Suspicious for Malignancy and Malignant category as Positive (Category C). Whereas highest specificity (100%) and PPV (100%) was achieved when considering only Malignant category as Positive (Category A). The highest Diagnostic Accuracy (95.04%) was achieved when Suspicious and Malignant category were considered as Positive (Category B). Our results are consistent with other similar studies.\textsuperscript{5,8, 19,20}

Among the benign category, Fibrocystic changes was most common. Misdiagnosis of malignant cases as benign /atypical could be due to scant cellularity of ductal epithelial cell with mild atypia and presence of scant bare bipolar cell in the background. Most lesions included in atypical category were benign phyllodes. In the suspicious category, most of the cases were diagnosed as Invasive Ductal Carcinoma, No Special Type. One case diagnosed as suspicious of Malignancy in FNAB shows presence of apocrine cell in dyscohesive clusters, fragments as well as scattered singly with cells exhibiting nuclear pleomorphism, overlapping and overcrowding. This case was diagnosed as Apocrine Carcinoma in Histopathology. (Figure 3a and 3b) Similarly, another case in suspicious category in FNAB shows presence of abundant extracellular mucin along with branching capillaries and few cells in fragments and dispersed singly exhibiting mild nuclear atypia. In histopathology this case came out to be Mucinous Carcinoma. (Figure 4a and 4b) The higher number of cases in the suspicious category in our study could be due to insufficient material in terms of quality and quantity. Among the Malignant category, all cases were diagnosed as Invasive Ductal Carcinoma, No Special Type.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/3a.png}
\caption{FNAC shows apocrine cells in fragments with nuclear pleomorphism, overlapping and overcrowding (400X).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/3b.png}
\caption{H&E stained section shows Apocrine Carcinoma. Tumor cells are seen in lobules and island separated by fibrocollagenous septa (200X).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/4a.png}
\caption{FNAC shows abundant mucin with branching capillaries and few dispersed cells (400X).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figures/4b.png}
\caption{H&E section showing Mucinous Carcinoma. Tumor cells are seen in nest and clusters floating within abundant extracellular mucin separated by fibrous septa (200X).}
\end{figure}
Malignancy, in the IAC Yokohama System allows classification of borderline lesions like Atypical Ductal Hyperplasia as they carry a higher risk of developing malignancy than benign lesion. The IAC Yokohama System for breast cytology provides a uniform reporting system with greater reproducibility.

CONCLUSION

IAC Yokohama System is a standard tool for diagnosing Breast FNAB with greater reproducibility of report and better communication between Pathologist and Clinicians. Specificity was highest when only the Malignant category was considered as Positive whereas Sensitivity was highest when Atypical and Suspicious category was also considered as Positive. The Diagnostic Accuracy was highest when Suspicious and Malignant category were included in the Positive result. This indicates IAC Yokohama as a standard reporting system for Breast FNAB yielding maximum diagnostic accuracy.

RECOMMENDATION

We recommend multicentric study with larger number of patients.

LIMITATIONS OF THE STUDY

Our study is limited by being a single center study with a limited number of patients. So, we cannot generalize our research findings to the general population in the region.

ACKNOWLEDGEMENTS

We are thankful to Dr Tara Kafle, Assistant Professor, Department of Community, Birat Medical College Teaching Hospital for her guidance during the sample size calculation and the statistical analysis.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURE

None

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