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Diagnostic Significance of "Intermediate Lesion" in Breast Cytology: Is the Risk of Malignancy Underestimated?

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Abstract: ***This study aims to evaluate diagnostic significance of C3 and C4 categories as per IAC Yokohama system and to assess the risk of malignancy (ROM) of these lesions with histopathological correlation. The archived Papanicolaou and Giemsa-stained smears of 400 FNAC cases of breast lump over a period of one year from June 2019 to May 2020 were retrieved. Cases were categorized as per IAC Yokohama Standardized reporting of breast fine needle aspiration cytology into 5 categories. The smears of atypical, probably benign (C3) and suspicious, favour malignancy (C4) was reviewed for detailed cytomorphological features and histopathology correlated with cytology diagnoses. Risk of malignancy (ROM) was calculated for Code 3 & 4 category. Possible causes for erroneous reports in cases of cyto-histo discrepancy and diagnostic significance of IAC Yokohama category C3 and C4 for clinical management was analysed. The ROM in Code 3 and Code 4 was 60% and 93%. The sensitivity, specificity, positive predictive value, and negative predictive value of C3 category in the diagnosis of benign lesions among intermediate cases were 40%, 92.61%, 80%, and 66.6% respectively. Similarly, sensitivity, specificity, positive predictive value, and negative predictive value of C4 category in the diagnosis of malignancy among intermediate cases were 92.3%, 40%, 66.6%, and 80% respectively. Risk of malignancy in the intermediate category is higher hence all the cases should be evaluated and managed appropriately. There are very few lesions fall under the grey zone lesions. By categorizing them it will be helpful for the cytopathologist to make right call for clinician to facilitate the triage and take early intervention on these patients.***

Keywords: Grey Zone, FNAC, IAC Category, Risk of Malignancy

1. Introduction

Female breast cancer is reported to be a leading cause of global cancer in 2020. It is one of the most diagnosed cancers with estimated incidence of 2.3 million new cases each year. It is the fifth leading cause of cancer mortality worldwide, with 685, 000 deaths (Sung Het al., 2020) . Breast lump is the commonest presenting symptom of breast cancer. Prompt evaluation of breast lump for diagnosis is very crucial in every case as breast lumps encompass not only malignancies, but also many different benign lesions. Early diagnosis helps in better management of the case, reduces undue anxiety of the patient in benign cases and reduce morbidity and mortality in malignant lesions (Jain et al., 2015) . The 'Triple approach' is an excellent tool for pre-operative diagnosis of breast lumps consisting of clinical assessment, radiological imaging and breast cytology (Chauhan et al., 2019).

Fine Needle Aspiration Cytology (FNAC) has a significant role in diagnosing breast lumps with low cost and shortest turnaround time allowing treatment decisions immediately. A standardized IAC Yokohama system for reporting breast cytology is proposed by IAC 'breast group' is thought to improve the performance of FNAC and provide a basis for quality assurance measures (Field et al., 2017) . The System has established five defined categories in order to bring a degree of uniformity to the diagnostic reporting (Wong et al., 2019) . The proposed a five-category classification is Code 1 (C1): insufficient material; Code 2 (C2): benign; Code 3 (C3): atypical, probably benign; Code 4 (C4): suspicious for malignancy, probably in situ or invasive carcinoma; and Code 5 (C5): malignant (Montezuma & Schmitt, 2019) . Categories such asC1, C2, and C5 are generally straightforward to pathologists. However, C3 and C4 categories where differentiation between atypical and suspicious lesions is required on cytology, constitute a grey zone and are prone for erroneous diagnosis (Arul et al., 2016) . Few authors have clubbed the two categories and classified them as 'equivocal' (Howell, 1999; Kanhoush et al., 2004) . The present study aims to evaluate diagnostic significance of C3 and C4 categories as per IAC Yokohama system and to assess the risk of malignancy (ROM) of these lesions with histopathological correlation.

2. Materials and Methods

This is a retrospective study carried out at the Department of Pathology in a tertiary care hospital at Mumbai. Study was done over a period of one year from June 2019 to May 2020

during which data of 10 years from February 2011 to January 2021 was analysed. Ethics clearance was obtained from the Institute's Ethics Committee for the study. The archived Papanicolaou and Giemsa-stained smears of 400 FNAC cases of breast lump in this period were reviewed blindly by two independent pathologists. Cases were categorized into the IAC Yokohama Standardized reporting of breast fine needle aspiration cytology into 5 categories and designated Code 1 – Insufficient material, Code 2 – Benign, Code 3 – Atypical, probably benign, Code 4 – Suspicious, probably in situ or invasive carcinoma, Code 5 – Malignant (6). Inadequately preserved smears, smears with handling artefacts and categories C1, C2 and C5 were excluded. Clinical and Imaging findings were obtained from the Electronic medical records. The cases categorised in Code 3 and 4 with complete clinical information and imaging findings were further analysed in this study. The smears of atypical, probably benign (C3) and suspicious, favour malignancy (C4) was reviewed for detailed cytomorphological features. Triple assessment by clinical examination, mammography and cytology is routinely performed in each case for management as per the hospital protocol. Histopathology from subsequent operations by excisional biopsy or mastectomy specimens on these cases were reviewed and correlated with cytology diagnoses. Risk of malignancy was calculated as [number of confirmed malignant cases/total number of cases] for Code 3 & 4 each. Possible causes for erroneous reports in cases of cyto-histo discrepancy and diagnostic significance of IAC Yokohama category C3 and C4 for clinical management was analysed.

3. Results

Total 400 cytology smears were classified based on IAC Yokohama standardized reporting of breast cytology into 5 categories. The distribution of cases in each category was as per Chart 1 with Code 2 being the commonest diagnosis followed by Code 5. Cases of Code 3-atypia, probably benign and Code 4-suspicious were 11 and 13 respectively (3%).

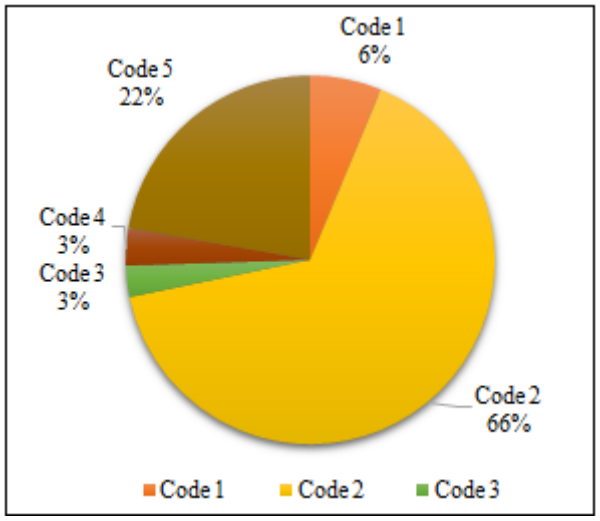

Chart 1: Distribution of breast cytology in IAC category

Histopathological diagnosis was available in 10 cases in C3 and 13 cases in C4 for correlation. One case was lost to follow up.

Analysis of C3 and C4 cases:

Code 3: Out of total 400 cases, 11 cases (3%) were categorised as 'atypia-probably benign'. Cytomorphological features in these cases were predominantly of benign lesion with single cluster of intact cell dispersal/nuclear enlargement and pleomorphism/high cellularity/necrosis/complex architecture suggestive of micropapillary or cribriform proliferation.

One case was lost to follow up and remaining 10 cases underwent excision for tissue diagnosis. On histology, 4 cases were benign with diagnoses-benign phyllodes, fibroadenoma with ductal hyperplasia, benign intraductal papilloma with ductal hyperplasia an acute mastitis. Of the 6 cases which showed malignant histology, 2 cases were intraductal papillary carcinoma, one case of encapsulated papillary carcinoma with invasion and remaining 3 cases of invasive breast carcinoma, no special type. Important observation noted in this study was that 4 (36%) out of 11 cases of Code 3 showed cytomorphological features of papillary lesions.3 were malignant papillary lesions and one was benign papilloma on histology.

Table 1: Risk of malignancy in Code3 category:

Category	Benign histology	Malignant histology	Total number of cases	Risk of malignancy
Code 3	4	6	10	60%

The ROM in Code 3 was 60% (Table 2).

Code 4: 13 cases (3%) were diagnosed as 'suspicious of malignancy probably in situ or invasive carcinoma' out of total 400 cases. Smears showed some of the cytological features usually found in malignant lesions, but with insufficient malignant features either number or quality to make definite diagnosis of malignancy.

All the cases of Code 4 underwent excision. Out of 13 cases, 12 showed malignant histology. Malignant cases were-11 cases of invasive breast carcinoma NST and one case of encapsulated papillary carcinoma with invasion. Single case of benign histology showed inflammation, reactive atypia with lactational changes and was diagnosed as acute mastitis in a lactating female.

Table 2: Risk of malignancy in Code 4 category

Category	Benign histology	Malignant histology	Total number of cases	Risk of malignancy
Code 4	1	12	13	93%

ROM in Code 4 was 93% (Table 3).

Table 3: Correlation of cytology and histology for Code 3 and 4:

Histopathological diagnosis	Cytology category		Total
	C 3	C 4	
Benign	4 (40%)	1	5
Malignant	6	12 (92%)	18
Total	10	13	23

There was a significant statistical difference between the number of benign and malignant diagnoses for categories C3 (40%) and C4 (92%) ($P < 0.001$). The sensitivity, specificity, positive predictive value, and negative predictive value of C4 category in the diagnosis of malignancy among

equivocal cases were 92.3%, 40%, 66.6%, and 80% respectively. Similarly, sensitivity, specificity, positive predictive value, and negative predictive value of C3 category in the diagnosis of benign lesions among equivocal cases were 40%, 92.61%, 80%, and 66.6% respectively.

4. Discussion

The use of core needle biopsy (CNB) is increasing for diagnosing breast lesions, most Low and Middle Income Countries (LMIC) continue to use FNAC as their first choice in the investigation of breast lesions in both screening and symptomatic population (Kocjan et al., 2008) . FNAC becomes integral part of diagnosis of breast cancer due to its distinct advantages like cost effective, easy to perform, short turnaround time with better diagnostic accuracy and curative relief in some cases like aspiration of a cyst (Mitra & Dey, 2015) (Ariga et al., 2002) (Rosa et al., 2020) . However, uniformity in reporting, differentiating some benign or borderline lesions from malignant lesions and subtyping of certain benign breast lesions are the challenges in breast cytology. The International Academy of Cytology (IAC) Breast Group was brought together with the aim of developing an internationally recognized and standardized reporting system that would define best practice guidelines for the use of FNAC in diagnosing breast lesions more consistently and accurately. The System has established uniform terminology for five defined categories for breast FNAC with stratified associated risk of malignancy (ROM) and management recommendations (Wong et al., 2019) . Studies in literature have proved that reporting of categories C1, C2, and C5 is straightforward with high specificity. The two intermediate categories (C3 and C4) are challenging as they lack specific clear criteria for diagnosis (Bibbo & Abati, 1996; Kanhoush et al., 2004; Mitra & Dey, 2015) . A significant number of malignant breast tumors are diagnosed as C3 and C4 categories. Currently, there is no individual morphological criterion that cytological diagnostics of malignant breast tumors could be based on; hence, there isa need for constant evaluation of cytological diagnostics results.

The patients age group in this study were ranging from 30 years to 80 years is similar to studies done by Arun et al., Dayal S et al., Ljiljana e (Arul et al., 2016; Dayal et al., 2021; Vuckovic et al., 2018) . Our study, we had 6% (24/400) cases in C3 and C4 categories which was consistent with other studies done by Arul et al and Dayal S et al which had given a range of 4%–17.7% for both (Arul et al., 2016; Dayal et al., 2021) . In Present study C3 was seen in 46% and C4 in 54% of the patient. The possible reason for the smaller number of cases might be because of specified population group with good follow up, better clinical and radiological correlation. We had almost 90% and 100% of histopathology reports in C3 and C4 category respectively. This highest percentage in our study may be due to early intervention, facility for guided aspirations in suspicious cases could be reasons for relatively higher percentage of cases in our study.

In C3 category we had 10 out of 11 cases with histopathology report. Remaining 1case was elderly patient who lost to follow-up subsequently. Out of 10 cases where histopathology was available, 4 cases showed benign histology. Benign cases were diagnosed on histopathology as benign phyllodes, fibroadenoma with ductal hyperplasia, benign intraductal papilloma with ductal hyperplasia and acute mastitis. Overlapping cytological features are reported between proliferative breast lesions, such as usual epithelial hyperplasia, intraductal papilloma's and fibroadenomas, and low-grade in situ lesions and low-grade invasive carcinomas. The distinction between cellular fibroadenomas and low-grade phyllodes tumors based on stromal hypercellularity and stromal atypia is problematic due to the varying cellularity, atypia and mitotic counts in each phyllodes tumors (Field & Rcpa, 2018) . Moreover, cytology aspirates cannot also properly distinguish between benign, borderline, and malignant phyllodes tumors (Study et al., 2013) . The key to correctly diagnose benign lesions with atypia and differentiation from low grade malignancies is the strict application of key cytological features diagnostic for specific lesions, including the assessment of smearing patterns, the architecture of tissue fragments and the degree of nuclear atypia (Field & Rcpa, 2018) . Of the 6 cases which showed malignant histology, final diagnosis of 3 cases were invasive breast carcinoma NST, 2 cases of duct carcinoma in situ-papillary (intraductal papillary carcinoma), one case of encapsulated papillary carcinoma with invasion. The specific diagnosis of low grade duct carcinoma in situ (LGDCIS) and lobular carcinoma in situ (LCIS) and the exclusion of invasive carcinoma in these cases is not possible in FNA cytology, but recognition of their features can suggest the diagnosis and help to distinguish in situ lesions from proliferative lesions to prevent a false positive diagnosis as carcinoma and a false negative diagnosis as a proliferative lesion (Field & Rcpa, 2018) . Out of total 11 cases of Code 3, 4 cases showed features of papillary lesions on cytology.3 were malignant papillary lesions and one was benign papilloma. Papillary lesions of the breast are difficult to diagnose on cytology posing dual challenge of distinction of the papillary lesions from the other nonpapillary lesions like fibroadenoma and the distinction of a benign from a malignant papillary lesion. Some of the papillary lesions are impossible to distinguish by cytology, such as intracystic or solid variants of papillary carcinoma. Cytology smears of papillary lesions are highly cellular, with epithelial cell clusters, singly scattered epithelial cells, and papillary fronds, sometimes with a true fibrovascular cores, some complex and branching papillae. The singly scattered cells have a columnar look or sometimes they look plasmacytoid with eccentric nuclei and moderate to abundant amount of cytoplasm. The background of such lesions is equally important and is characterized by foamy macrophages, apocrine cells, and bipolar cells in a fluid backdrop. The presence of macrophages, apocrine cells, and bipolar cells is associated with a benign papillary lesion rather than a malignant one. In addition, a malignant papillary lesion is more often associated with a higher degree of cellularity, a greater number of singly scattered cells, and more complex papillae with fibrovascular cores. Atypia can be seen in both benign and malignant papillary lesions and is not a discriminating feature. Proper classification of a papillary lesion is not always possible even by core needle biopsy and subsequent histopathology (Mitra & Dey, 2015) . ROM in Code 3 was calculated to be 60% in our study. This is significantly higher than other studies done by Montezuma

et al., (13%) Wong et al., (15.7%) and Hoda et al., (51.5%) (Montezuma & Schmitt, 2019) (Wong et al., 2019) (Hoda & Brachtel, 2019) . Our study had lesser number of cases categorized in this category. A specified population group with good follow up, better clinical and radiological correlation, early intervention, facility for guided aspirations in suspicious cases could be reasons for relatively higher percentage of malignant cases in our study. Though this category with relatively lower ROM than subsequent categories could appear challenging for a cytopathologist to interpret, inclusion of cases with abnormal cytological findings in this category can facilitate the triage and adequate treatment of patients (Rosa et al., 2020) . The suggested management options for Code 3 include to repeat the FNAC or to perform a CNB, or to review the patient with imaging at 3–6 months, with subsequent repeat FNAC or CNB if the lesion has changed on imaging. If imaging and CNB are not available, repeat FNAC and close follow-up are recommended (Field & Rcpa, 2018) .

In C4 category, there were 13 cases in this category in our study. All the cases of Code 4 underwent excision. Out of 13 cases, 12 showed malignant histology. Out of these 12 malignant cases, 11 cases were invasive breast carcinoma NST, and one case was encapsulated papillary carcinoma with invasion. Most of the cases of invasive breast carcinoma NST also showed features of low-grade DCIS, UDH and ADH on histology. The causes of a "suspicious of malignancy" diagnosis is like those of the atypical category and include technical problems related to the skill of the operator performing the FNAC, making smears and handling the material, the experience of the interpreting cytopathologist, and the nature of the breast lesion. The cytological features of proliferative lesions and low-grade or in situ carcinomas overlap and great care must be taken in assessing smear patterns and nuclear atypia. Low grade DCIS includes a range of solid, cribriform, micropapillary, papillary and solid papillary subtypes, and it may be associated with microcalcifications without producing a clinical or radiological mass. Cytology cannot specifically diagnose low grade DCIS and at the same time exclude invasive carcinoma. Cytological findings of highly cellular smears, a pattern of large tissue fragments showing cribriform, micropapillary or papillary architecture, a variable but often marked increase in dispersed single cells showing mild to moderate nuclear atypia, a greatly reduced number or total lack of myoepithelial cells associated with the epithelial tissue fragments, and scant or absent bare bipolar nuclei in the background suggest a diagnosis of DCIS. Whereas high grade DCIS has been reported to be associated with extensive necrosis, calcifications, and high-grade nuclear atypia in dispersed single epithelial cells and both small and larger crowded epithelial tissue fragments. The smears are often low in cellularity reflecting the small volume of cancer cells in ducts relative to breast tissue (Field & Rcpa, 2018) . Only discordant case in this category on cytology showed features of abundant inflammation, reactive atypia of ductal epithelial cells, apocrine changes on dirty background in a lactating female. In view of large, progressively increasing lump and suspicious radiological (BIRAD 4) and cytological changes, the lesion was excised. Histopathologically, the lesion was diagnosed as acute mastitis with lactational changes. Breast FNA from a pregnant or lactating woman often poses a diagnostic challenge. In cytology, a cellular smear with a dispersed/discohesive population of cells with round nuclei, coarse chromatin or hyperchromatic chromatin, and prominent nucleoli raises a suspicion of malignancy. Careful observation for numerous naked nuclei, cells containing multivacuolated cytoplasm, scattered inflammatory cells and foamy macrophages, and a bubbly proteinaceous background often helps the cytopathologists toward the right diagnosis. Sometimes malignancy can be associated with lactation, and lactation in such a situation masks the evidence of malignancy therefore it is advisable to categorize such lesions into uncertain categories to avoid false negative diagnosis (Mitra & Dey, 2015) **.** Risk of malignancy in this category was 93% in our study. All the other studies have also reported higher ROM for this category. ROM in study by Montezuma et al (97.1%) and Tejaswini et al (100%) and ROM of Wang et al (84.6%) and Hoda et al (85.4%) (Hoda & Brachtel, 2019) were slightly lower (Montezuma & Schmitt, 2019) (Tejeswini et al., 2021) (Wong et al., 2019) (Hoda & Brachtel, 2019) . A "suspicious of malignancy" FNAC cytology diagnosis should lead to review of the imaging findings, and further biopsy or excision is an absolute requirement (Field & Rcpa, 2018) .

The sensitivity, specificity, positive predictive value, and negative predictive value of C4 category in the diagnosis of malignancy among intermediate cases were 92.3%, 40%, 66.6%, and 80% respectively which is comparable to other studies (Arul et al., 2016; Dayal et al., 2021; Kapil et al., 2022; Yusuf et al., 2014) Table 4.

Table 4: Statistical comparison of our study with other studies:

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Yusuf et al	76.7	76.5	85.2	65	<0.001
Arul et al	84.8	86.7	86.2	64.3	<0.001
Dayal S et al	81.48	50	68.7	64.2	Not done
Kapil R et al	83.33	87.5	90.91	77.78	<0.001
Present study	92.3	40	66.6	80	<0.001

Similarly, sensitivity, specificity, positive predictive value, and negative predictive value of C3 category in the diagnosis of benign lesions among equivocal cases were 40%, 92.61%, 80%, and 66.6% respectively.

Most of the patients preoperatively diagnosed with C3 category, have more chances for benign pathological conditions, while in C4 category, chances for breast cancer are higher.

Table 5: Comparison of Risk of malignancy with other studies

Histopathological diagnosis	Arul et al		Goyal et al		Kapil R et al		Present study	
	C3	C4	C3	C4	C3	C4	C3	C4
Benign	64.3	13.8	62.5	12.5	78	9	40	0
malignant	35.7	86.2	37.5	87.5	22	90	60	100

5. Conclusion

Risk of malignancy in the intermediate category is higher hence all the cases should be evaluated and managed appropriately. Careful observation of cytology aspirates can minimize the incidence of grey zone lesions. There are very few lesions fall under the grey zone lesions. By categorizing them it will be helpful for the cytopathologist to make right call for clinician to facilitate the triage and take early intervention on these patients.

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