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A review of the predictive values and malignancy risks of the YOKOHAMA system for reporting breast fine needle aspiration cytology

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Abstract
Background: FNA reliably diagnoses breast lesions without surgery. Radiologists, surgeons, and oncologists can quickly communicate cytology results with a standardized care plan. The 2017 IAC conference in Yokohama established a comprehensive breast cytology system. This research examined the distribution of fine needle aspiration (FNA) cytology of breast lesions using the Yokohama 5 categories and the risk of malignancy (ROM) and predictive values of breast cytology using the International Academy of Cytology (IAC).
Method: The study was conducted in the cytology laboratory of the Center of Early Detection of Breast Cancer, Oncology Teaching Hospital, Medical City Complex, Baghdad. A total of 108 consecutive patients were included in the study, and slides were collected for each patient.
Results: Most patients were symptomatic and 45.9 years old. 23 (21.3%) lesions had inadequate material and were C1, whereas 14 (13%) had benign-looking epithelium and were C2. 37 (34.3%) instances exhibited mild to moderate nuclear atypia, whereas 4 (3.7%) had paucicellular smears but notable atypia and were C4. Thirty C5 lesions (27.8%) were malignant. C3 had 5.4% ROM, C4 75%, and C5 100%. Three settings determined predicted values. Group A exclusively considered C5 instances positive, with a sensitivity of 85.7%, specificity and positive predictive value (PPV) of 100%, and NPV of 77.3%. Group B regarded C4 and C5 instances as positive, with sensitivity of 94.3%, specificity of 94.1%, NPV of 88.9%, and PPV of 97.1%. With 100% sensitivity and 67.3% PPV, Group C deemed C3, C4, and C5 cases positive.
Conclusion: The FNA had the greatest specificity (100%), sensitivity (100%), and accuracy (94.2%) when C4 and C5 were positive. The research emphasizes the need for a standardized breast cytology system to facilitate communication between radiologists, surgeons, and oncologists.

Keywords: A review, predictive values, malignancy, risks, YOKOHAMA system, breast, FNA, cytology

Introduction
Fine needle aspiration (FNA) is a well-established method for nonsurgical diagnosis of breast lesions, first reported in 1920 by Hayes Martin and James Ewing [1]. While core needle biopsy (CNB) has become more common due to its ability to provide information on tissue architecture and differentiate between in situ and invasive lesions, FNA remains a valuable diagnostic tool when CNB is not available [1]. Given the multidisciplinary nature of managing breast lesions [2], it is essential to have organized and easily communicable cytology reports that can be shared with radiologists, surgeons, and oncologists to facilitate effective treatment planning. The International Academy of Cytology (IAC) developed a comprehensive structured system for conducting and reporting breast cytology, which was established during a conference held in Yokohama in 2017 [3]. This system aims to serve as a global reference for the accurate identification of breast lesions using FNA cytology. The Center of Early Detection of Breast Cancer at the Oncology Teaching Hospital, along with a few other centers, adopted the Yokohama system in 2018 [4]. In this study, the primary objective was to analyze the distribution of FNA cytology results of 108 consecutive breast lesions over five months, according to the Yokohama 5 categories. Additionally, the study aimed to assess the risk of malignancy (ROM) and predictive values of breast cytology using this newly implemented system. Aims of the study: To study the distribution of FNA cytology of breast lesions according to Yokohama 5 categories and to assess the risk of

malignancy (ROM) and predictive values of breast cytology using the new International Academy of Cytology (IAC) system.

Method

This retrospective study aimed to assess the distribution of FNA cytology results of breast lesions according to the Yokohama 5 categories and evaluate the risk of malignancy (ROM) and predictive values using the International Academy of Cytology (IAC) system. The study was conducted at the Center of Early Detection of Breast Cancer in the Oncology Teaching Hospital, Medical City Complex, Baghdad. A total of 108 FNAB breast cases from consecutive patients were collected during the period from January 2022 to May 2022. The cytology slides for each patient, ranging from 3 to 5 slides, were reviewed and categorized according to the Yokohama system under the supervision of a supervisor. Matching histopathology data were available for 52 cases, including 28 cases from core needle biopsy, 19 cases from surgical biopsy, and 5 cases from cell blocks. The aim was to compare the cytology reports of categories C3-5 with the corresponding histopathology results to determine concordance or discordance. Ethical approval for the study was obtained from the Medical City Directorate and Oncology Teaching Hospital ethical committees. The FNA procedure was performed using a 21-22G needle attached to a 10 ml disposable syringe. Ultrasound guidance was used to localize the mass, and negative pressure was created and maintained in the syringe during aspiration. The obtained material was smeared directly onto slides, which were then stained using a modified Papanicolaou staining method. Statistical analyses were conducted using IBM SPSS software version 25. Descriptive statistics such as mean, standard deviation, range, frequency, and percentage were used to summarize the data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall test accuracy were calculated to assess the performance of the cytology results. By analyzing the data, the study aimed to provide insights into the distribution of FNA cytology results and evaluate the effectiveness of the IAC system in predicting malignancy in breast lesions.

Results

The mean age of the patients was 45.9 year ranging between 18 and 78 years? About more than half of the patients were in the fourth and fifth decades. Family history of breast cancer and other cancers was reported by 24 (22.2%) and 17 (15.7%) of the patients respectively. Seven (6.5%) of the patients were a known case of breast cancer and were on regular follow-ups while the majority 101(93.5%) were symptomatic. The most frequent complaint was a breast lump in 77 (71.3%) followed by pain in 29 (26.9%). Nipple discharge was a presenting feature in 2 (1.9%). An underlying mass was identified by ultrasound for both those with pain and nipple discharge. Patient's characteristics are summarized in Table 1.

Table 1: Patients characteristics.

Patient characteristic	Frequency	Percentage
Age groups		
≤ 30	12	11.1
31-40	22	20.4
41-50	34	31.5
51-60	30	27.8
> 60	10	9.3
Family history of breast ca	24	22.2
Family history of other malignancy	17	15.7
Personal history of breast ca	7	6.5
Presentation		
Diagnostic	101	93.5
Follow up	7	6.5
Chief complaint		
Pain (with ultrasound identified lesion)	29	26.9
Mass	77	71.3
Nipple discharge (with ultrasound identified	2	1.9
lesion)		

The lesions were slightly more in the left breast 58 (53.7%), approximately half of them were in the upper outer quadrant of the breast (UOQ). FNA was performed under an ultrasound guide for all of the cases. Histopathology was available for 52 (48.1%) patients, 28 (53.8%) were from core needle biopsy and 19 (36.5%) were surgical, (Table 2).

Table 2: Breast lesion characteristics.

Lesion characteristic	Frequency	Percentage
Laterality		
Right	50	46.3
Left	58	53.7
Site		
UOQ	55	50.9
LOQ	7	6.5
RA	30	27.8
LIQ	5	4.6
UIQ	11	10.2

Cell block	5	9.6
CNB	28	53.8
Excisional	9	17.3
Mastectomy	10	19.2
Total biopsy	52	48.1

Abbreviations: UOQ, upper outer quadrant; LOQ, lower outer quadrant; RA, retro-areolar; LIQ, lower inner quadrant; UIQ, upper inner quadrant; CNB, core needle biopsy

The distribution of breast lesions according to Yokohama system categories as figure 1 shows, 23 (21.3%) of the lesions revealed smears without mammary epithelium and were categorized as C1, 14 (13%) lesions revealed smears containing benign looking epithelium and were categorized as C2. Lesions with mild to moderate nuclear atypia were reported in 37 (34.3%). Four (3.7%) lesions revealed paucicellular smears but mammary epithelium showed marked atypia and were categorized as C4. 30 (27.8%) of the lesions revealed smears unequivocal for malignancy were categorized as C5.

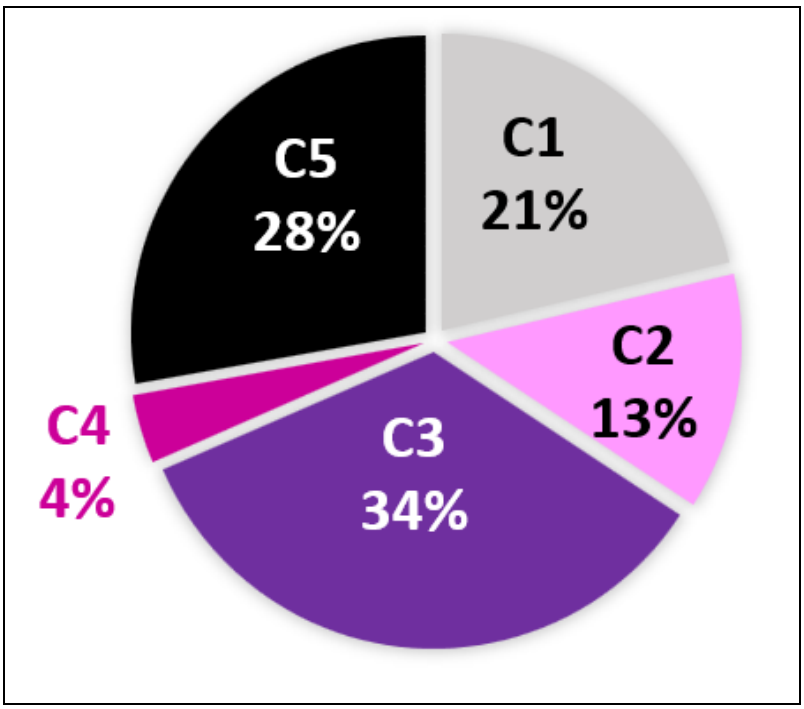

Fig 1: Pie chart illustrating the distribution of breast lesions according to Yokohama system categories.

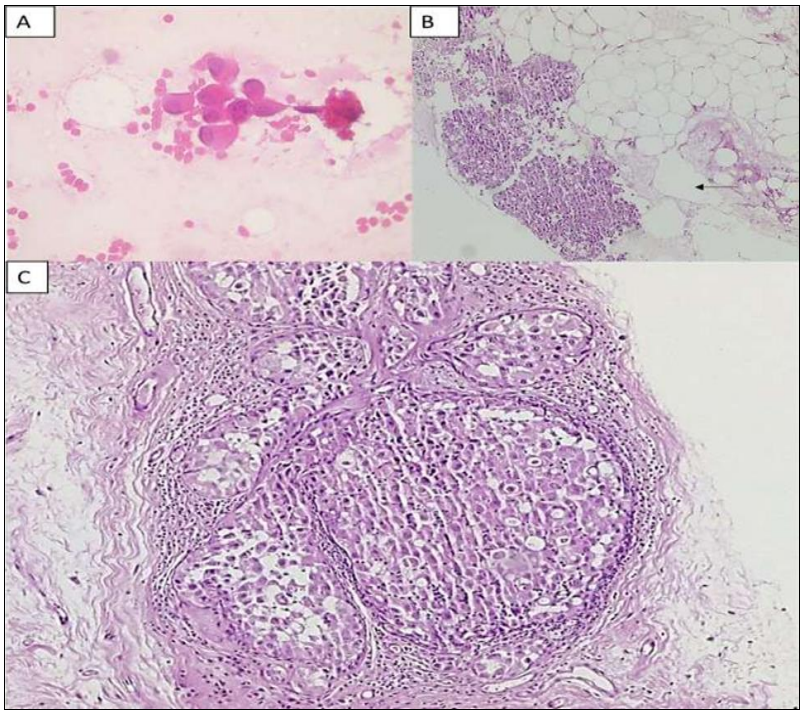

Fig 2: Histopathology- cytology images of a C5 lesion A) cytology revealed discohesive cells with eccentric nuclei, X400 magnification B) lobular carcinoma invading the adipose tissue C) Lobular in situ, X100 magnification.

Risk of malignancy (ROM) was calculated for 52 lesions that were histopathologically confirmed in addition to 19 cases in the C3 category which were kept on radiological follow-up. Because lesions in C1 and C2 had no histopathology diagnosis, calculation of the cancer rate in these categories was not possible. As Table 3.3 showed, ROM in C3 was 5.4% and 75% in C4 and 100% in C5.

Table 3: Risk of malignancy in Yokohama system categories

Category	Total No	Cancer No	ROM
C3	37	2	5.4%
C4	4	3	75.0%
C5	30	30	100.0%
Total	71	35	49.3%

Abbreviations: ROM, rate of malignancy

To calculate the predictive value, three groups were constructed. Group A included C5 cases only as positive test; here the true positive tests were 30 out of 35 total positive confirmed by histopathology giving the test a sensitivity of 85.7% with a PPV of 100%. The test predicted all the true negative cases giving a specificity of 100% with a NPV of 77.3%. Group B considered cases in C4 and C5 categories as positive test; this group has higher sensitivity of 94.3% because the number of true positive tests was 33out of 34 histopathologic ally confirmed ca. There were 16 true negative tests out of 18 total negative tests giving group B a NPV of 88.9%. Group C considered cases in C3, C4, and C5 as positive tests, this group had a perfect sensitivity of 100%, however, specificity and NPV could not be calculated because histopathology for true negative cases (C2) were lacking. Group B had the highest test accuracy, Table (4).

Table 4: Predictive values of the Yokohama system

Predictive values	Group A (C5 as positive)	Group B (C4 and C5 as positive)	Group C (C3 and C4 and C5 as positive)
Sensitivity	85.7%	94.3%	100%
Specificity	100%	94.1%	NA
PPV	100%	97.1%	67.3%
NPV	77.3%	88.9%	NA
Accuracy	90.4%	94.2%	NA

Abbreviation: NA, not applicable.

Discussion

Fine needle aspiration (FNA) of the breast is a valuable tool for distinguishing malignant tumors from benign processes, particularly when combined with radiology. Although it has been largely replaced by core needle biopsy (CNB) due to CNB's ability to assess the histological grade and hormone condition, FNA remains important, especially in regions where CNB is not readily available [5]. In recent years, there has been a growing recognition and reaffirmation of breast FNA in both developed and low- to middle-income countries following the International Academy of Cytology (IAC) summit in Yokohama, which recommended standard reporting systems [6]. In this retrospective study, 108 FNA cases reported according to the IAC Yokohama system were collected. The distribution of categories was as follows: 21% were categorized as C1 (insufficient material), 13% as C2 (benign), 34% as C3 (atypical), 4% as C4 (suspicious), and 28% as C5 (malignant). The rates of C4 and C5 were similar to those reported in a study by De Rosa *et al*., while the rates of C2 and C3 were relatively reversed. The variation in the rate of C1 reporting (ranging from 3.6% to 19.2%) can be attributed to differences in the definition of this category by various institutes and the presence of radiological correlation [7]. In the present study, a relatively high proportion of C1 cases were inflammatory lesions, and the reports included a clear statement of inflammation to avoid unnecessary repeats. The rate of C3 category in this study was higher than in previous studies, and it was mainly attributed to fibroadenoma and fibrocystic changes with mild to moderate atypia. Fibroadenomas can exhibit high cellularity, singly dispersed cells, and variable degrees of nuclear enlargement and pleomorphism, which can prompt their categorization as C3. Similarly, proliferative fibrocystic lesions, such as usual ductal hyperplasia and sclerosing adenosis, can generate highly cellular smears with features that resemble low-grade ductal carcinoma in situ (DCIS) or invasive cancer, making C3 categorization necessary [3]. The risk of malignancy (ROM) in this study was 5.4% for C3, 75% for C4, and 100% for C5. When compared to other studies, the ROM of C3 was lower, which could be attributed to the inclusion of all C3 cases, including those that did not undergo surgery. Honda *et al*., in a review of 27 studies with a total of 33, 341 FNAs, found that ROM for inadequate material, benign, atypical, suspect, and malignant categories were 30.3%, 4.7%, 51.5%, 85.4%, and 98.7%, respectively. The overall sensitivity and specificity were 96.3% and 98.8%, respectively [8]. They highlighted that depending on histopathology to determine ROM may overestimate rates for inadequate, benign, and atypical categories due to selection bias, while assessing ROM through histopathologic and clinical follow-up may underestimate rates [8]. The study also evaluated the predictive values of the FNA cyt ology results. The highest sensitivity (100%) was achieved when considering atypical, suspicious, and malignant cases as positive findings (Group C). However, including atypical cases in the positive findings resulted in a lower positive predictive value (PPV). When only malignant cases were considered as positive (Group A), the best specificity (100%) was observed. The highest diagnostic accuracy (96.4%) was achieved when both suspicious and malignant cases were included as positive findings (Group B). These findings align with previous studies [8, 9]. Other studies have reported a range of sensitivity and specificity values for each group. For Group A, sensitivity ranged from 65.4% to 86.7%, and specificity ranged from 95.9% to 100%. In Group B, sensitivity ranged

from 79.5% to 96%, and specificity ranged from 58.1% to 99.8%. In Group C, sensitivity ranged from 84.6% to 98.9%, and specificity ranged from 46.3% to 86% [8-10]. Previous studies conducted in Iraq reported similar sensitivity (84.4% to 87.3%) and specificity (97.1% to 100%) values for FNA in diagnosing breast cancer [11, 12].

Conclusion

The text provides data on the rates of cases and risk of malignancy in different types of lesions (C1-C5). The highest risk of malignancy was found in C4 and C5 lesions, with a 100% risk in C5. The accuracy of FNA was highest when considering C4 and C5 as positive, with a specificity of 100% when only considering C5 as positive and a sensitivity of 100% when considering C3, C4, and C5 as positive.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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