Review Article

The Yokohama System for Reporting Breast Cytopathology

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Abstract

The International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy Cytology was developed by a group of expert cytopathologists and clinicians in the breast field. Five categories are defined to stratify breast lesions by their risks of malignancy and managed accordingly. Clinical and radiologic information (triple test) are critical for further management. Ultrasound guidance, and rapid on-site evaluation are valuable for improving the rate of definitive diagnosis. Ancillary studies can be tested on cytologic samples to provide prognostic, predictive information as well as diagnostic clues. Based on many published studies in different institutions worldwide, the implementation of the system appears to have been successful. However, further studies are important for improvements and modifications to the current system.

Introduction

The International Academy of Cytology (IAC) Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy (FNAB) Cytology was developed by a group of expert cyto-pathologists and clinicians in the breast field.[1,2] The work started following a meeting at the Yokohama International Congress of Cytology in 2016. The goals of the system are to standardize the reporting of breast cytology, improve communication between cytopathologists and clinicians, and facilitate optimal patient care.

Breast FNAB is a simple, fast, and cost-effective procedure that can provide a rapid and accurate diagnosis with minimal complications. In developing countries, it is widely used, representing one of the most commonly performed FNAB procedures.[3] The reported sensitivity is 91–92% and the specificity is approximately 98% in two meta-analyses.[4,5]

The studies selected in those meta-analyses were based on a set of rules including an assessment of the risk of bias; most of the studies were retrospective[6–11] while a few were prospective.[12,13] For the diagnosis of breast carcinoma, the positive predictive value (PPV) is particularly high, in the range of 99–100%.[5] In developed countries, where medical resources are more readily available, as a component of the "triple test" (the other two are clinical information and imaging information), FNAB cytology has a PPV close to 100%.[14] However, FNAB has intrinsic limitations in that it is unable to assess invasion status (*i.e., in situ* vs. invasive carcinoma) and intact histologic architecture. Although in many institutions, core needle biopsy (CNB) has been gradually replacing FNAB, CNB should be used as a complementary rather than a replacement procedure. At MD Anderson Cancer Center, FNAB of breast lesions is still a part of standard care, especially in the evaluation of satellite lesion(s) surrounding an index breast cancer, local-regional lymph nodes, and lesions likely to be benign (such as cystic lesions and infectious processes) based on clinical and radiology findings. FNAB of the breast can be performed either under ultrasound guidance or by palpation. Ultrasound-guided FNAB may be performed by either radiologists or pathologists. Rapid On-Site Evaluation (ROSE) has the advantage in that it can reduce rates of insufficient, atypical, and suspicious diagnoses, and thus increase the rate of definitive diagnosis in benign and malignant categories.[10] ROSE can also provide direct feedback for the person performing the FNAB. For radiologist-performed FNAB, ROSE allows for communication between the radiologist and cytopathologist during the procedure. The results of ROSE can guide the collection of appropriate material for further evaluation such as cell block, CNB, microorganism culture, or flow cytometric immunophenotyping.

It is important to emphasize that a successful FNAB procedure and definitive diagnosis requires well-trained personnel for performing aspiration, preparing smears, and final interpretation. The IAC Yokohama system utilizes the following five categories: (1) insufficient/inadequate, (2) benign, (3) atypical, (4) suspicious for malignancy, and (5) malignant to stratify the risk of malignancy (ROM) based on the most recent literature (subject to future modification) and suggested management.

In the standardized report, one of the specific diagnostic categories should be listed as a diagnostic heading. Furthermore, a brief cytologic description and concise conclusion are recommended and in the conclusion, a specific diagnosis is desired when feasible. Otherwise, the most likely diagnosis may be given with a differential diagnosis. The "atypical" category is included in the system to achieve a high negative

Table 1. Five diagnostic categories of the Yokohama system

Category	ROM, 95% CI, %	Management	ROSE
Insufficient	10–28	Review clinical/radiologic findings; if clinical/imaging findings are indeterminate or suspicious, repeat FNAB or proceed to CNB; if clinical/imaging findings are benign or low-risk, short-term clinical follow-up may be considered	At ROSE, either repeat FNAB up to 3 times or proceed to CNB
Benign	1–3	Review clinical/radiologic findings; if the "triple test" findings are benign, no further biopsy is required; if clinical/imaging findings are indeterminate or suspicious, repeat FNAB or proceed to CNB	At ROSE, if cytology findings do not explain clinical/radiologic findings, either repeat FNAB up to 3 times or proceed to CNB
Atypical	17–23	Review clinical/radiologic findings; if atypia is likely due to technical issue, repeat FNAB or proceed to CNB; otherwise, proceed to CNB	At ROSE, if atypia is likely due to technical issue, repeat FNAB or proceed to CNB; otherwise, proceed to CNB
Suspicious	79–92	Review clinical/radiologic findings; if not index lesion, surgical excision may be considered at the time of surgery; otherwise, CNB is mandatory	At ROSE, may proceed to CNB
Malignant	99–100	Review clinical/radiologic findings; CNB is recommended	At ROSE, may proceed to CNB

ROM, risk of malignancy (based on meta-analysis by Nikas *et al*.[5]); FNAB, fine-needle aspiration biopsy; CNB, core-needle biopsy; ROSE, rapid on-site evaluation. The recommended management listed here is based on where imaging and CNB are available.

predictive value (NPV) for a "benign" diagnosis. Similarly, the "suspicious for malignancy" category is designed to preserve the high PPV for the "malignant" category. Detailed ROM and management (summarized in Table 1)[5] will be further discussed in each category.

The Yokohama reporting system

Insufficient/inadequate

Definition: The smears are too sparsely cellular or too poorly smeared or fixed to allow for a cytomorphological diagnosis.

Individual practice should select either "insufficient" or "inadequate" and use it consistently. The term "non-diagnostic" is not recommended by the system. The reason for using this category should always be stated in the report. Whether a sample is regarded as "insufficient/inadequate" or not should be based on the assessment of the material on the slides along with the clinical and radiologic findings. A sparse sample without epithelial cells may be considered adequate if the cytologic findings can explain the clinical/radiologic findings, such as a cystic lesion that is completely collapsed after aspiration, abscess, fat necrosis, scar tissue, or an intramammary lymph node. However, if information for the triple test is not available, a recommendation to correlate with clinical and imaging findings should be stated.

When sampling a solid mass, it is proposed that seven epithelial groups each consisting of at least 20 cells are required to properly evaluate the cellular arrangement and myoepithelial cells. It should be noted that some lesions such as lobular carcinomas may yield very limited tissue fragments with only a few dispersed atypical cells. In those conditions, even if the cellularity is low, it should be categorized as "atypical". Similarly, any significant nuclear atypia or tumor necrosis, in an otherwise inadequate aspirate, may be regarded as "atypical".

The inherent qualities of the lesion can significantly influence the inadequate rate. Small, sclerotic, less proliferative, mobile, impalpable, or poorly defined lesions tend to have higher inadequate rates. Furthermore, the FNAB operator and the availability of ROSE can also affect the inadequate rates. It is, therefore, recommended to provide proper training

and ongoing mentoring of FNAB operators including smear techniques. Additionally, if possible, ultrasound guidance and ROSE, (three passes when ROSE is not available)—are also recommended. It is further recommended that experienced FNAB operators should aim for inadequate rates of less than 5%. An inadequate rate of greater than 20% requires urgent review and improvement of the techniques.

The reported inadequate rates in the literature vary widely from 0.7% to 47%, due to a variety of factors including the definition of inadequacy, the experience of the operators, patient cohorts, types of practices, types of lesions, and availability of ROSE.[3] Therefore, it is difficult to establish an accurate ROM for this category, and it is estimated to be 10–28% based on the recent meta-analysis.[5] Additionally, most studies excluded this category from the calculation of PPV and NPV.

If the smears are technically suboptimal, repeat aspiration should be performed, ideally with ultrasound guidance and ROSE. Further management of an inadequate breast FNAB is dependent on the clinical and radiologic findings. If the imaging is indeterminate or suspicious, repeat sampling (either FNAB or CNB) is required. When the imaging suggests a benign or low-risk process, clinical and radiologic follow-up may be considered appropriate, usually in 3–6 months.

Benign

Definition: A benign breast FNAB diagnosis is made in cases that have unequivocally benign cytologic features, which may or may not be diagnostic of a specific benign lesion.

The exact cytologic features of benign lesions depend on the specific underlying condition. The most common benign breast lesions include fibrocystic changes, fibroadenoma, intraductal papilloma, usual ductal hyperplasia, gynecomastia, fat necrosis, intramammary lymph node, and normal breast tissue with terminal ductal-lobular units. Relatively less common benign breast lesions include mastitis and abscess, granulomatous mastitis, lactational change, sclerosing adenosis, and collagenous spherulosis. The main cytologic findings of those entities are further discussed.

Fibrocystic changes often show apocrine sheets, small cohesive ductal epithelial tissue fragments, foamy histiocytes, and a proteinaceous background. A cystic lesion may
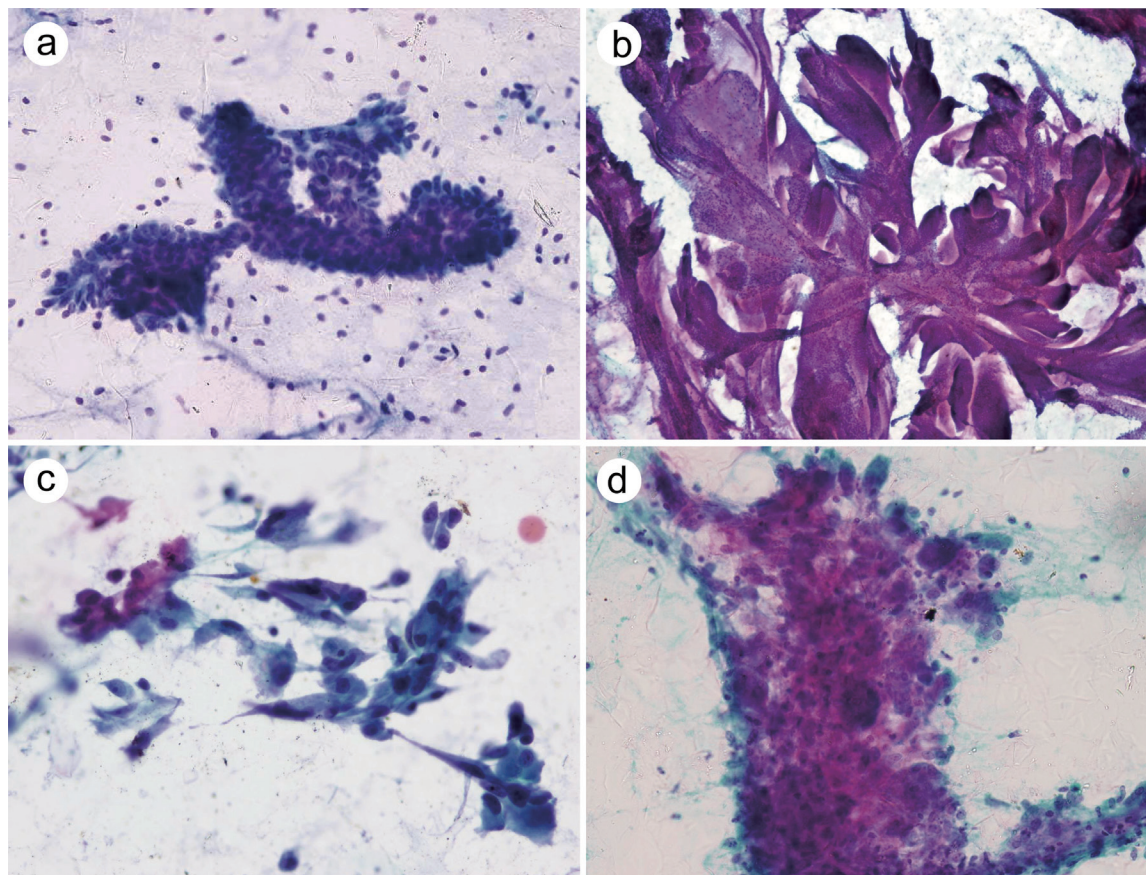
Fig. 1. Cytomorphology of representative benign breast lesions. (a) Fibroadenoma shows three-dimensional clusters of ductal epithelial cells with an antler-like configuration and many dispersed bipolar myoepithelial cells or small naked nuclei in the background (×200). (b) Intraductal papilloma shows papillary structure of ductal epithelial cells with fibrovascular cores and some background dispersed myoepithelial cells (×40). (c) Reparative changes in a case of fat necrosis. The presence of cellular atypia may lead to overinterpretation (×400). (d) Granulomatous mastitis shows multinucleated giant cells, macrophages, mixed inflammatory cells, and debris (×400).

show only a granular proteinaceous background without any epithelial cells. Correlation with clinical and radiologic findings is particularly important and the finding of a collapsed cyst after aspiration is usually indicative of a benign cyst. Fibroadenoma typically shows large monolayered sheets or three-dimensional clusters with an antler-like configuration in a background of bipolar cells, small naked nuclei, and occasional fibrillar stromal fragments (Fig. 1a). Intraductal papilloma typically shows moderate to high cellularity with cohesive papillary groups and many discohesive cells. Myoepithelial cells are typically abundant, and fibrovascular core, proteinaceous material, apocrine cells, and histiocytes may be identified (Fig. 1b). Usual epithelial hyperplasia shows large cohesive ductal epithelial cells with myoepithelial cells in a clean background. The large tissue fragments show features of streaming with irregular slit-like lumina and mild nuclear atypia. Gynecomastia often shows a low cellularity with hyperplastic ductal epithelial cells admixed with myoepithelial cells; bare bipolar nuclei and scant fibrillary stromal fragments may be seen in the background. Fat necrosis may show degenerated fat cells, granular multicolored debris, myospherulosis, foamy histiocytes, and multinucleated giant cells. Reactive changes may be seen due to repair (Fig. 1c). Intramammary lymph nodes show mixed lymphoid population. Acute mastitis and abscess show abundant neutrophils and scattered foamy histiocytes, in a background of necroinflammatory debris. Re-

current subareolar abscess may show keratinous debris and multinucleated giants. Granulomatous mastitis shows granulomas and multinucleated giant cells with possible necrosis (Fig. 1d).[15] Lactational changes may show small epithelial clusters or discohesive cells with mild nuclear enlargement, fine chromatin and prominent single central nucleoli, granular and vacuolated cytoplasm with many stripped nuclei in a granular/proteinaceous background (Fig. 2a). Sclerosing adenosis may show small cohesive terminal ductal epithelial groups with myoepithelial cells and dense stromal tissue in a background of scattered bare bipolar nuclei and isolated epithelial cells. Small angulated tubules may be seen, which may be mistaken for low-grade breast carcinoma, especially tubular carcinoma (Fig 2b, c).[16] Additionally, collagenous spherulosis may be encountered, in which spherical hyaline globules are associated with cohesive clusters of myoepithelial cells (Fig. 2d). The features may somewhat resemble adenoid cystic carcinoma.

The reported ROM for this category ranges from less than 1% to 3%, with an NPV greater than 97%).[5,9,11] The triple test is important for guiding clinical management. If a benign FNAB diagnosis explains the clinical and imaging findings, routine follow-up is appropriate, usually in 12–24 months. When the imaging findings are indeterminate or suspicious, repeat sampling, usually by CNB, should be recommended. Additionally, FNAB or CNB should be performed when a lesion shows significant changes during follow-up.
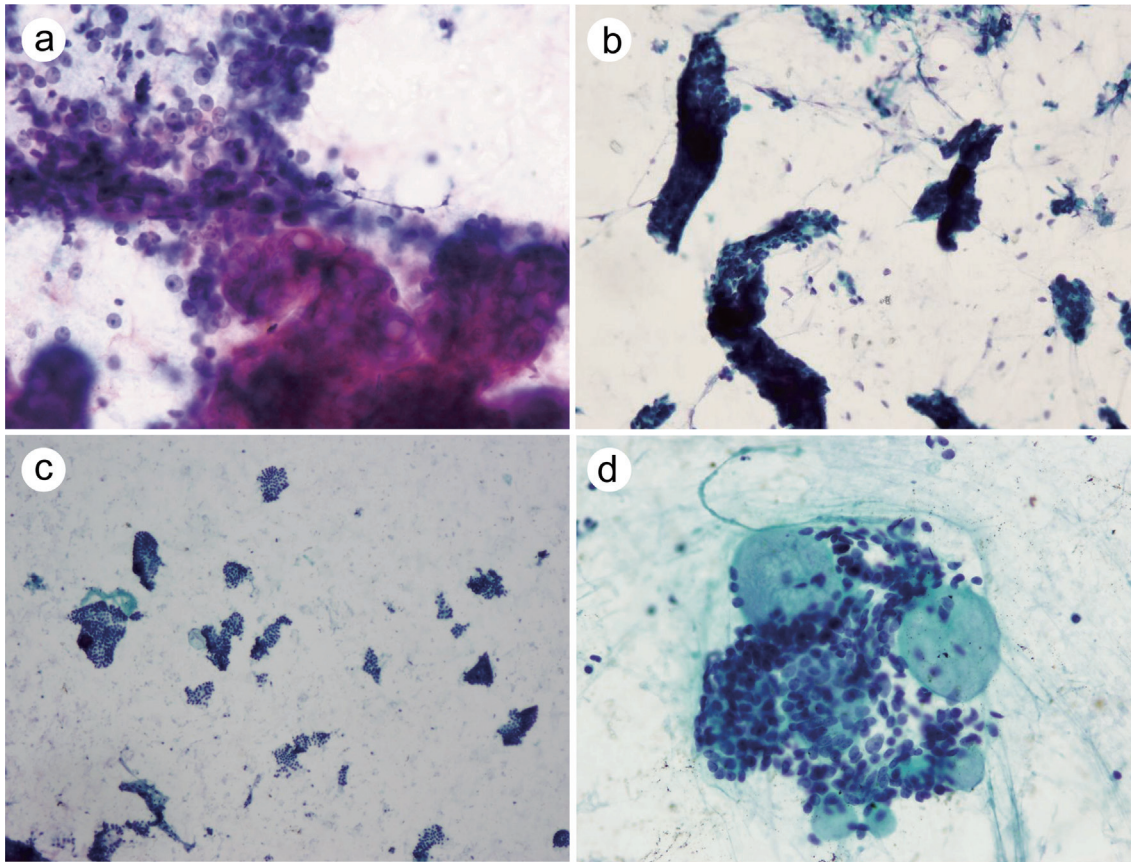
Fig. 2. Cytomorphology of additional representative breast lesions. (a) Lactating adenoma shows vacuolated and granular cytoplasm, round nuclei with fine chromatin and prominent single central nucleoli, and many stripped nuclei in a granular proteinaceous background (×400). (b) Sclerosing adenosis shows small cohesive clusters of ductal epithelial cells with scattered background bare bipolar nuclei. The angulated tubules may mimic tubular carcinoma (×100). (c) Tubular carcinoma shows a few angulated tight clusters of ductal epithelial cells with rigid borders and sharp points. Myoepithelial cells are essentially absent (×40). (d) Collagenous spherulosis shows spherical homogenous acellular hyaline globules surrounded by clusters of bland myoepithelial cells. The features can be mistaken for adenoid cystic carcinoma (×400).

Atypical

Definition: The term atypical in breast FNAB cytology is defined as the presence of cytologic 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 common cytologic features associated with the "atypical" category include numerous single intact cells, nuclear enlargement and pleomorphism, high cellularity, the presence of necrosis or mucin, and complex micropapillary and cribriform architectural features. When possible, the most likely diagnosis and a list of differential diagnoses should be provided in the report.

The common factors contributing to an "atypical" diagnosis include suboptimal aspiration and smear preparation skills that lead to low cellularity, cellular distortion and artifacts, and interpretive difficulties. However, the nature of a lesion is often an important contributory factor. For example, a sclerotic or fibrotic lesion may result in an atypical diagnosis, even for the most experienced pathologist.

Some breast lesions intrinsically show significant overlap in their morphologic features resulting in difficulty in distinguishing them based on cytologic findings, sometimes even on histologic findings of a small biopsy. The examples include distinguishing benign proliferative lesions from atypical intraductal/lobular hyperplasia or low-grade carcinoma (either in situ or invasive), distinguishing fibroadenoma from low-grade phyllodes tumor, and distinguishing low-grade in situ carcinoma from low-grade invasive carcinoma. Knowledge of the key cytologic features and spectrum of those entities may help to reduce the frequency of "atypical" diagnoses.

For cases with follow-up CNB or excision, the ROM of an "atypical" diagnosis is reported to be in the range of 22% to 39%.[3,17] Studies utilizing the IAC Yokohama System had a ROM of 17% to 23% based on a recent meta-analysis.[5]

The underlying reasons for an atypical diagnosis should be taken into account for its management. If the atypical diagnosis is found to be primarily due to technical problems, repeat sampling is recommended. In the case of interpretative difficulty, a correlation with clinical and radiologic findings should be performed. If the radiologic and clinical findings are indeterminate or suspicious, a repeat sampling, ideally by CNB, is required. In situations where neither clinical nor radiologic information is available, follow-up with imaging in 3–6 months and/or repeat sampling should be considered. If the lesion has changed during follow-up, repeat FNAB or CNB is recommended.

Suspicious for malignancy

Definition: The term "suspicious for malignancy" in breast FNAB is defined as the presence of some cytomorphological features that are usually found in malignant lesions, but with
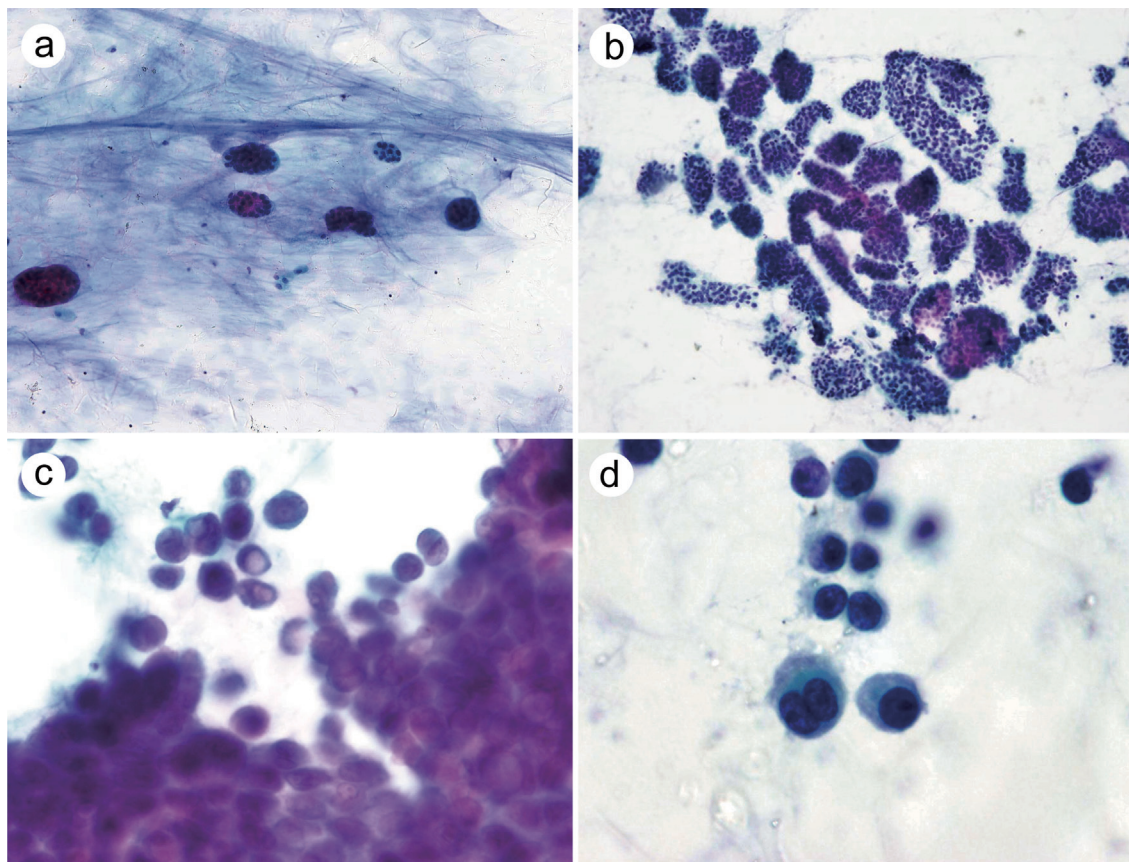
Fig. 3. Cytomorphology of representative malignant breast lesions. (a) Mucinous carcinoma shows tight three-dimensional clusters of bland tumor cells in a background of mucin (×100). (b) Micropapillary carcinoma shows many cohesive papillary clusters with occasional tight angulated borders. Fibrovascular cores are absent and cellular atypia is variable (×100). (c) Invasive lobular carcinoma typically shows loosely arranged plasmacytoid cells occasionally with intracytoplasmic vacuoles simulating signet-ring cells of upper gastrointestinal origins (×400). (d) Metastatic melanoma in the breast shows large atypical cells with plasmacytoid features, binucleation, and prominent nucleoli. The features may overlap with lobular carcinoma (×400).

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.

Like the "atypical" diagnosis, there are significant variations in the use of the "suspicious for malignancy" category among different cytopathologists and the factors causing the "suspicious for malignancy" category are similar to those contributing to an "atypical" diagnosis. The creation of the "suspicious for malignancy" category is to maintain the high PPV of the "malignant" category.

One of the common lesions associated with the "suspicious for malignancy" category is ductal carcinoma in situ (DCIS), including both low-grade DCIS and high-grade DCIS. Additionally, low-grade invasive ductal carcinoma, lobular carcinoma (both *in situ* and invasive), and some benign proliferative lesions can be associated with this category.

For cases with follow-up CNB or excision, the ROM of a "suspicious" diagnosis is reported to be in the range of 60% to 95%.[3,17] Studies utilizing the IAC Yokohama System showed a ROM of 79% to 92% for this category, based on a recent meta-analysis.[5] The cases within this category are mandatory for histologic confirmation, usually by CNB. An excisional biopsy is required if CNB is not available.

Malignant

Definition: A malignant cytological diagnosis is an unequivo-

cal statement that the material is malignant, and the type of malignancy identified should be stated whenever possible.

A malignant diagnosis should only be rendered when there is a full constellation of supportive cytological features. The common features associated with malignancy on FNAB include high cellularity, discohesive epithelial cluster or numerous dispersed single cells, and nuclear atypia (such as nuclear enlargement, pleomorphism, crowding, and overlapping) without significant myoepithelial cells. However, none of these features, when taken separately, is diagnostic for carcinoma. For instance, low-grade carcinoma may show bland nuclear features while carcinoma with desmoplastic reaction or sclerotic stroma may yield a low cellularity specimen.

Whenever possible, the type of malignancy (such as ductal, lobular, mucinous, micropapillary, *etc*.) should be mentioned or at least suggested in the report (Fig. 3a–c). It is also important to keep in mind that lymphoma, melanoma, angiosarcoma, and metastatic carcinoma can be seen in the breast and should be sometimes considered in the differential diagnosis (Fig. 3d).

The reported PPV of a malignant lesion by FNAB ranges from 92% to 100%.[3,17] Recent studies utilizing the IAC Yokohama System showed a ROM of 99% and 100% for this category.[5] In the developed world, when combined with the triple test, the PPV should exceed 99%. If the triple test is discordant, a CNB (occasionally excision biopsy) is mandatory before clinical treatment starts.
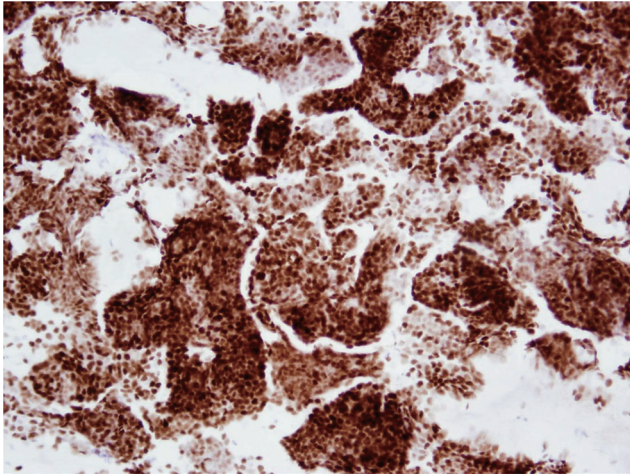
Fig. 4. ER immunostaining performed on a Papanicolaou-stained smear shows diffuse and strong positivity in an axillary lymph node (×100). ER, estrogen receptor.

When the malignant cytologic diagnosis is concordant with the radiologic and clinical findings, and material is available for prognostic and predictive biomarker testing, clinical management may start based on the corresponding results, especially in low- and middle-income countries. However, as FNA samples cannot reliably distinguish *in situ* carcinoma from invasive carcinoma, the standard practice is to perform biomarker testing on CNB or resection specimens. When enlarged/abnormal loco-regional lymph nodes are detected by imaging during the same procedure, FNAB may be performed for staging purposes.

Ancillary tests in breast cytology

In this section, we summarize the main ancillary tests used in breast cytology.

Prognostic/predictive markers

The most important prognostic and predictive markers for breast carcinoma include estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67.[18] These markers are typically performed on histologic sections of newly diagnosed primary breast carcinoma. In cytology practice, ER, PR, and HER2 tests on FNA samples may be requested by a clinician in metastatic breast carcinoma to assess the stability of these markers when comparing with the status of a primary counterpart, and thus guide further treatment.[19,20] Cell block section is an ideal sample type to perform immunocytochemical study because the sample processing is similar to that of histologic section.[21–23] However, when cell block is not available, ER and PR can be tested on Papanicolaou-stained smear as long as in-house validation has been performed (Fig. 4).[24,25] ER and PR staining results on direct smears have shown high concordance compared to histology specimens.[24,26] HER2 status can also be reliably tested via fluorescence *in situ* hybridization (FISH) using either cell block or direct smear (in MD Anderson Cancer Center, Diff-Quik stained smear is used for FISH).[19] HER2 immunostaining on smear is not reliable since membranes of tumor cells are often stripped off.

Diagnostic Ancillary Testing

In cytology practice, one of the most common scenarios is to confirm a breast origin in a metastatic setting. ER is frequently used for this purpose. In addition, GATA3 and a recently emerged marker, trichorhinophalangeal syndrome type 1 (TRPS1),[27,28] have been found to be highly sensitive and relatively specific for metastasis of breast origin. Both markers are useful if primary breast carcinoma is triple-negative. These markers are preferred in cytology practice because they demonstrate nuclear staining patterns and are easy to interpret.[29,30] However, since these markers are not entirely specific, correlation with clinical, radiologic, and cytologic findings is very important. Occasionally, myoepithelial markers may be tested on cell block section of a breast lesion to help distinguish benign proliferation from carcinoma, for example, papilloma vs. papillary carcinoma.

Conclusions

Breast FNAB is wildly used in developing countries as a simple, fast, and cost-effective procedure. Even in resource-rich developed countries, FNAB can be a valuable tool in the evaluation of satellite lesions surrounding an index breast cancer, local-regional lymph nodes, and lesions likely to be benign. The triple test is important for an accurate cytology interpretation while ultrasound guidance and rapid on-site evaluation are valuable for improving the rate of definitive diagnosis. Ancillary studies can be tested on cytologic samples to provide prognostic, predictive information as well as diagnostic clues.

Five categories of the IAC Yokohama System for Reporting Breast FNAB Cytology aim to stratify breast lesions by their ROMs and manage them accordingly. Many studies have been published to implement this reporting system in different institutions worldwide. While most of those studies are retrospective, the implementation of the system appears to have been successful in standardizing the reporting and improving diagnostic accuracy. However, more prospective studies would be essential to further validate the system.

Conflict of interest

The manuscript was submitted during Dr. Yun Gong's term from June 2021 to June 2023 serving as an editorial board member of the *Journal of Clinical and Translational Pathology*. The authors have no other conflict of interests to declare.

Author contributions

Study concept and design (WY and YG), manuscript writing (WY, QG, and YG), and critical revision (WY, QG, and YG). All authors have made a significant contribution to this study and have approved the final manuscript.

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