Review

ACTA CYTOLOGICA

Acta Cytologica 2019;63:257–273
DOI: 10.1159/000499509

Received: February 10, 2019
Accepted after revision: March 7, 2019
Published online: May 21, 2019

The International Academy of Cytology Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy Cytopathology

Andrew S. Field[a] Wendy A. Raymond[b] Mary Rickard[c] Lauren Arnold[d] Elena F. Brachtel[e] Benjaporn Chaiwun[f] Lan Chen[g] Luigi Di Bonito[h] Daniel F.I. Kurtycz[i] Andrew H.S. Lee[j] Elgene Lim[k] Britt-Marie Ljung[l] Pamela Michelow[m, n] Robert Y. Osamura[o, p] Maurizio Pinamonti[q] Torill Sauer[r] Davendra Segara[s] Gary Tse[t] Philippe Vielh[u] Phek Y. Chong[v] Fernando Schmitt[w]

[a]Department of Pathology, St Vincent's Hospital, and University of NSW and University of Notre Dame Medical Schools, Sydney, NSW, Australia; [b]South Australian Pathology, Department of Surgical Pathology, Flinders Medical Centre, Flinders University of South Australia, and Clinpath, Adelaide, SA, Australia; [c]BreastScreen NSW and Faculty of Health Sciences, University of Sydney, Sydney, NSW, Australia; [d]Sydney Breast Clinic, Sydney, NSW, Australia; [e]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [f]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [g]Pathology Department, Beijing Hospital, National Center of Gerontology, Beijing, PR China; [h]Department of Anatomical Pathology, University of Trieste, Trieste, Italy; [i]Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Wisconsin State Laboratory of Hygiene, University of Wisconsin, Madison, WI, USA; [j]Department of Histopathology, Nottingham University Hospitals, Nottingham, UK; [k]Connie Johnson Breast Cancer Research Laboratory, Garvan Institute of Medical Research, St Vincent's Hospital, UNSW Medical School, Sydney, NSW, Australia; [l]Department of Pathology, University of California San Francisco, San Francisco, CA, USA; [m]Department of Anatomical Pathology, University of the Witwatersrand, Johannesburg, South Africa; [n]National Health Laboratory Service, Johannesburg, South Africa; [o]Nippon Koukan Hospital, Kawasaki, Japan; [p]Keio University School of Medicine, Tokyo, Japan; [q]Department of Pathology, Cattinara Hospital, Trieste, Italy; [r]Institute of Clinical Medicine, Department of Pathology, Faculty of Medicine, Akershus University Hospital, University of Oslo, Oslo, Norway; [s]Breast Surgical Oncologist, St Vincent's Private Hospital, Sydney, NSW, Australia; [t]Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, Sha Tin, Hong Kong SAR; [u]Laboratoire National de Santé, Departement de Pathologie Morphologique et Moleculaire, Dudelange, Luxembourg; [v]Department of Pathology, Sengkang General Hospital, SingHealth Duke-NUS Academic Medical Centre, Singapore, Singapore; [w]Institute of Molecular Pathology and Immunology, Instituto de Investigação e Inovação em Saúde and Medical Faculty, University of Porto, Porto, Portugal

Keywords
Breast cytology · Fine-needle aspiration biopsy · International Academy of Cytology · Reporting system · Yokohama

Abstract
The International Academy of Cytology (IAC) gathered together a group of cytopathologists expert in breast cytology who, working with clinicians expert in breast diagnostics and

E-Mail karger@karger.com
www.karger.com/acy

Prof. Andrew S. Field
St Vincent's Hospital
390 Victoria Street, Darlinghurst
Sydney, NSW 2010 (Australia)
E-Mail Andrew.field@svha.org.au

management, have developed the IAC Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy (FNAB) Cytology. The project was initiated with the first cytopathology group meeting in Yokohama at the 2016 International Congress of Cytology. This IAC Yokohama System defines five categories for reporting breast cytology, each with a clear descriptive term for the category, a definition, a risk of malignancy (ROM) and a suggested management algorithm. The key diagnostic cytopathology features of each of the lesions within each category will be presented more fully in a subsequent atlas. The System emphasizes that the crucial requirements for diagnostic breast FNAB cytology are a high standard for the performance of the FNAB and for the making of direct smears, and well-trained experienced cytopathologists to interpret the material. The performance indicators of breast FNAB, including specificity and sensitivity, negative predictive value, positive predictive value and ROM stated in this article have been derived from the recent literature. The current practice of breast FNAB has evolved with the increasing use of ultrasound guidance and rapid on-site evaluation. Two recent publications have shown a range of ROM for the insufficient/inadequate category of 2.6–4.8%, benign 1.4–2.3%, atypical 13–15.7%, suspicious of malignancy 84.6–97.1%, and malignant 99.0–100%. The management algorithm in the System provides options because there are variations in the management of breast lesions using FNAB and core-needle biopsy in those countries utilizing the "triple test" of clinical, imaging, and FNAB assessment, and also variations in the availability of CNB and imaging in low- and middle-income countries. The System will stimulate further discussion and research, particularly in the cytological diagnostic features of specific lesions within each category and in management recommendations. This will lead to continuing improvements in the care of patients with breast lesions and possible modifications to the IAC Yokohama System.

Introduction

The International Academy of Cytology (IAC) System for Reporting Breast Fine-Needle Aspiration Biopsy (FNAB) Cytology has been developed following an initial meeting at the Yokohama International Congress of Cytology in 2016, by a group of cytopathologists, radiologists, surgeons and oncologists expert in the management of breast lesions [1]. The process included the writing of draft documents based on a review of the literature and the expertise of the members of the group, followed by discussion and review within the group. Minor modifications were made based on peer responses to an international questionnaire carried out in mid-2018 (hosted at the University of Wisconsin State Laboratory of Hygiene and Department of Information Technology using Qualtrics software [Provo, Utah]). Further discussion and editing then took place. This article is a brief summary of the proposed system.

The overarching aims of the System are to standardize and improve the reporting of breast cytology, establish best practice guidelines, improve training in the performance and interpretation of breast cytology, clarify communication between cytopathologists and breast clinicians and to link this reporting system with patient management so as to facilitate optimal breast care.

Since the National Cancer Institute consensus document was published following a 1996 conference in Bethesda, Maryland, USA [2], the role of FNAB has changed in the developed world reflecting the increasing role of core-needle biopsy (CNB) particularly in the setting of mammographic screening for breast cancer. In the developing world breast FNAB is one of the most common FNAB procedures and is increasingly used as a key element in the campaign to reduce breast cancer mortality rates [3–9].

Breast FNAB is a rapid, accurate and highly cost-effective diagnostic procedure with a minimal complication rate for the broad spectrum of benign and malignant breast lesions. It has a high sensitivity in the range of 90–95% and a high positive predictive value (PPV) approaching 100% for the diagnosis of breast carcinoma [10–17]. Breast FNAB has a low false negative rate with any errors related to diagnostic difficulties with low-grade carcinomas and sampling error, and a very low false positive rate, which is usually due to misinterpretation of fibroadenomas, intraductal papillomas and papillary lesions [16–18]. Breast FNAB in the developed world with a high level of medical resources is a component of the "triple test" comprising clinical, imaging and FNAB cytology, and the triple test has a PPV close to 100% [19].

Ideally, except in certain circumstances such as pregnancy, the vast majority of breast lesions should be assessed initially clinically and then by bilateral mammography and ultrasound, and, where required, by FNAB, which may be directed by ultrasound. Rapid on-site evaluation (ROSE) of the FNAB direct smears provides a reduction in insufficient rates, as well as a reduction in atypical and suspicious rates, and a concomitant increase in benign and malignant diagnoses [17]. ROSE also allows immediate triage of the lesion and, dependent on the

FNAB findings, CNB may then be utilized in an appropriate and cost-effective manner. There is a long and successful tradition of using palpation to direct the FNAB and this is totally appropriate where medical infrastructure and resources are not readily available, and, specifically, where access to ultrasound equipment is limited or not available.

FNAB cytology has faced challenges including the introduction of CNB, which should be regarded as a complementary rather than replacement test. The extrapolation of biopsy protocols developed in mammographic screening programs where the lesions are often small and frequently identified as calcifications without a mass lesion, to the work up of all breast lesions is inappropriate [20]. CNB offers advantages in definitively diagnosing invasive carcinoma, assessing mammographically detected calcifications and assisting with proliferative lesions, but similarly to FNAB, it is a sampling device. CNB is more invasive, time consuming, has a higher rate of complications, and has a greater cost for both the biopsy equipment and the required histopathological laboratory processing and reporting [16, 21, 22]. There are reports of a risk of track seeding by carcinoma [23], and of a possible worse prognosis after CNB [24].

Performing breast FNAB, making direct smears and interpreting the material does require specific training and on-going experience. In many institutions interventional cytopathologists performing the biopsy procedures have largely been replaced by radiologists due to practice patterns and in some cases disparities in reimbursement schedules. The number of breast FNAB procedures has significantly dropped in some institutions, reducing the experience and teaching potential for radiologists and pathologists [20]. The greatest quality assurance issue in providing a breast FNAB service is the quality of the technique of the FNAB proceduralist and the quality of the technique in the making of the direct smears. A cytopathologist performing and then interpreting the smears is at a great advantage to reach an accurate diagnosis [16, 25–27]. Liquid-based cytology has been utilized quite successfully but is more costly and many key diagnostic cytological findings are lost [28].

The IAC Yokohama Reporting System emphasizes the importance of skilled biopsy and smear making techniques to optimize quality and enhance FNAB diagnosis. The key elements to the breast FNAB procedure are the careful selection of a line of approach for the needle, fixation of the lesion by palpation or palpation around an ultrasound probe, and a rapidly performed puncture of the lesion using a rapid movement of the needle into and out from the immobilized lesion, with appropriate use of aspiration. Ultrasound can provide guidance and visualization of the needle tip throughout the procedure. Good training and continued monitoring are essential.

The System suggests that ideally both air-dried Giemsa-stained direct smears and alcohol-fixed Papanicolaou-stained slides should be prepared utilizing a method of splitting the material obtained on each needle pass. Routine rinsing of the needle or separate passes for cell block preparation to enable immunohistochemistry for prognostic indicators can be utilized [12, 29]. Liquid-based cytology preparations can also be considered [28].

The IAC Yokohama System has five categories that can be stratified by their risk of malignancy (ROM):

- Insufficient/inadequate
- Benign
- Atypical
- Suspicious of malignancy
- Malignant

The standardized structured report should state one of these five descriptive terms as a diagnostic heading [1]. A laboratory and its cytopathologists should select either "insufficient" or "inadequate" and use this term consistently. The term "non-diagnostic" is used in various reporting systems in different ways, and is not recommended. An FNAB report should always be correlated with the clinical and imaging findings in the triple test, and if there is a discrepancy, the FNAB should be categorized by the material on the slide and not as "non-diagnostic." In this situation, the report should contain a statement that the material may not be representative of the lesion seen on imaging and that further biopsy by FNAB or usually CNB is required. If imaging is not available, but the clinical findings and FNAB are discrepant, then the management is similar, that is, further biopsy is required.

The decision was made to include an "atypical" category in order to maximize the negative predictive value (NPV) of a "benign" diagnosis, and a "suspicious of malignancy" category to maximize the PPV of a "malignant" diagnosis. The majority of "atypical" cases will be benign proliferative lesions and the majority of "suspicious of malignancy" lesions (see sections below) will be in situ or low-grade carcinomas, although in both categories scant or poorly smeared limited material may prevent a more definitive diagnosis.

The structured report headed by a category term should then include a brief cytological description noting where possible the presence or absence of key diagnostic features, which will be detailed in the forthcoming IAC Yokohama System for Reporting Breast FNAB Atlas [1].

This description is followed by a conclusion or summary in which the cytopathologist should give as specific a diagnosis of the lesion as possible (for example, "fibroadenoma"), or, if the diagnosis is uncertain, provide the most likely differential diagnoses. Ideally, both the imaging and cytology findings should be as precise as possible to maximize the specificity of the triple test, and to highlight any discrepancies. Finally, a category number, 1, 2, 3, 4, or 5 for insufficient, benign, atypical, suspicious of malignancy, and malignant, respectively, can be stated in the body of the report. This category number will assist with quality assurance activities and research. The category number is not to be used as a replacement for the actual diagnosis or the descriptive category terminology. The aim of utilizing consistent categories and a clear diagnosis is to enhance communication between the cytopathologist and clinician.

The ROM for each category has been extracted from the most recent literature [16, 17], so as to include current best practice and minimize confounding differences between studies, which include patient cohorts, experience of the FNAB operators, use of ultrasound guidance and statistical analyses [15, 17]. The IAC Reporting categories were then linked with management algorithms, which are dependent on the availability of local medical resources and local practices (Table 1). To meet this challenge, management options have been provided. However, many studies in the literature have used different methodologies, statistical calculations and categories which do not align with the categories in the IAC System, so the current ROM will be refined by future research, analogous to the modifications of the Bethesda System for Reporting Thyroid FNAB Cytology [30].

Category: Insufficient/Inadequate

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

FNAB smears are regarded as adequate or inadequate based on the assessment of the material on the slides. If there is sufficient material on the slides to reach a diagnosis the FNAB is categorized based on that material. However, if the triple assessment is discrepant and the FNAB material does not explain the imaging or clinical findings, then the FNAB report should contain a statement that "the material may not represent the lesion," and further FNAB or usually CNB is required. The term "non-diagnostic" is not recommended.

The assessment of adequacy may not require epithelial material to be present if the cytological findings correlate with the clinical and imaging findings in the triple test and are sufficient to make a precise diagnosis [11, 13]. Such situations include: pus consistent with an abscess; a proteinaceous background with or without histiocytes consistent with cyst contents when the cyst has been drained under imaging or has no residual mass to palpation; fat tissue fragments consistent with a lipoma or fatty nodule; spindle cell lesions; fat necrosis; reactive lymphoid material consistent with an intramammary lymph node, or in some cases of a hyalinized fibroadenoma which correlates with imaging.

However, if there is a mass lesion on palpation or imaging, that does not decrease in size and drain on FNAB, it is recommended that seven tissue fragments each consisting of 20 or more epithelial cells to allow assessment of the architecture and the presence or absence of myoepithelial cells, should be a measure of adequacy [2, 13]. It is recognized that some epithelial lesions such as lobular carcinoma may on occasion yield only scant material and not provide tissue fragments of this size, but their pattern and cellular detail will usually allow them to be categorized as at least atypical [31–33]. 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 [13]. The reason for the categorization as insufficient/inadequate should always be stated in the report.

There are considerable variations in the literature in the definition of insufficient/inadequate and in the rates of insufficiency. These variations include the varying mix of patients, the experience of the FNAB operators, the type of practice (mammographic screening assessment clinic or clinic for patients with symptomatic lumps and other concerns) and types of lesions (palpable or impalpable), and it is not unexpected that insufficient rates also vary from 0.7 to 47% [10, 12, 14–17]. Similarly, an accurate ROM cannot be established because insufficient cases are usually excluded from PPV and NPV analyses, because only patients with surgical biopsy follow-up are included in these studies and the indication for surgery was often clinical or radiological suspicion of carcinoma [15, 17, 34].

When no clinical or imaging information is provided to the cytopathologist by those who have performed the FNAB, such as "completely drained cyst," and there is no reasonable opportunity to review the case with the clinician, it is recommended that a report should be issued with a caveat that "correlation with clinical and imaging findings is required because the FNAB findings may not represent the lesion."

Table 1. Management recommendations

Category	ROM[a], %	Management[b]	LMICMX[c]	Comment
Insufficient	2.6–4.8	Review clinical and imaging findings; if imaging indeterminate or suspicious, repeat FNAB or proceed to CNB; if imaging benign consider repeat FNAB	Review clinical findings; if suspicious repeat FNAB	At ROSE, if inadequate due to a technical issue or the material does not explain the clinical or imaging findings, repeat FNAB up to a total of 3 times, ideally using ultrasound guidance; if FNAB still insufficient, proceed to CNB
Benign	1.4–2.3	Review clinical and imaging findings; if "triple test" benign, no further biopsy required, and review depends on the nature of the lesion; if clinical and/or imaging indeterminate or suspicious, repeat FNAB or proceed to CNB	Review clinical findings: if benign, nothing further; if suspicious, repeat FNAB	At ROSE, if the cellular material does not explain the clinical or imaging findings, repeat FNAB, up to a total of 3 times, using ultrasound guidance; follow-up depends on the nature of the lesion, e.g., abscess – 2 weeks after antibiotics, fibroadenoma – 12 months; some centers review in line with screening program policy
Atypical	13–15.7	Review clinical and imaging findings; repeat FNAB if atypia considered likely to be due to a technical issue; if good material available and atypical, repeat FNAB or preferably proceed to CNB[d]	Review clinical findings and repeat FNAB; manage based on FNAB category; if further FNAB atypical, consider excisional biopsy	At ROSE, if atypia is considered due to a technical issue, repeat FNAB; if cellular material adequate and atypical, proceed to CNB
Suspicious	84.6–97.1	Review clinical and imaging findings; CNB is mandatory[e]	IF no CNB available, excision biopsy	At ROSE proceed to CNB
Malignant	99.0–100	Review clinical and imaging findings; CNB if any discrepant findings. If "triple test" is concordant and malignant, proceed to definitive management[f, g]	If no CNB available, excision biopsy	At ROSE may proceed to CNB

See text for further discussion. ROM, risk of malignancy; FNAB, fine-needle aspiration biopsy; CNB, core-needle biopsy; ROSE, rapid on-site evaluation.

[a] References: Montezuma et al. [16]; Wong et al. [17].

[b] Best practice recommendation where imaging and CNB available.

[c] Low- and middle-income countries management: best practice recommendations where imaging and/or CNB not available.

[d] Atypical cases with good material and atypical features should have clinical and imaging review: there is considerable variation in management protocols at this point, including immediate CNB if the imaging is atypical or indeterminate and review with imaging at 3 or 6 months if imaging is benign.

[e] If FNAB is "suspicious" or "malignant," then regardless of clinical and imaging findings, the FNAB dictates management.

[f] Concordant "triple test" is mandatory before surgery and prognostic markers can be performed on the cell block, but it is recognized that in some institutions CNB is required prior to neoadjuvant chemotherapy or definitive surgery, while in other institutions the patient will proceed to definitive surgery and prognostic markers will be performed on the excised specimen.

[g] FNAB with or without CNB is recommended on palpable or suspicious on ultrasound axillary lymph nodes to assist in staging the lesion.

The insufficient rate in breast FNAB is influenced by:

- the skill of the practitioner who performs the FNAB with cytopathologists and practices utilizing ROSE having the lowest rates of insufficiency [16, 25, 26, 27, 35]
- the skill of those making the direct smears, where problems include crush artefact, slow air-drying for Giemsa smears, slow placement in alcohol for Papanicolaou-stained smears and contamination with ultrasound gel
- the nature of the lesion with high insufficient rates in lesions of small size [26, 27, 36–39], lesions that are difficult to stabilize [40, 41], or scirrhous or sclerotic,

lowly proliferative or lowly cellular, such as lobular carcinomas, or lesions that are microcalcifications without a corresponding mass lesion [33, 42]
- the number of FNAB passes: two or three is recommended if ROSE is not utilized [43].

The insufficient rate can be reduced by better initial training, a greater case load to build experience, use of ultrasound guidance, immediate feedback on the adequacy and quality of the specimen through ROSE or a cytopathologist performing the FNAB, and rapid correlation with imaging and clinical findings [16, 17, 25, 35, 37]. It is recommended that experienced personnel performing the FNAB should aim for less than a 5% insufficient rate, particularly if utilizing ROSE, while a rate of 10–20% requires review of the procedure. If the rate is greater than 20% urgent review of the techniques of those performing the FNAB is required.

Management

If the smear is insufficient due to technical issues the FNAB should be repeated to a maximum of three passes [43]. If the insufficiency is due to a lack of sufficient cellularity to explain the clinical or imaging expected diagnosis, it should be repeated. Correlation with the clinical and imaging findings in the triple test determines further management. This is facilitated by the use of ultrasound guidance and ROSE. If the imaging is indeterminate or suspicious, repeat FNAB or CNB is mandatory. If the imaging is regarded as benign or at low risk, in some practices follow-up with clinical or imaging review may be regarded as appropriate and this usually occurs at 3–6 months. In a setting where no imaging is available, the clinical and FNAB findings should be closely correlated, and repeat FNAB usually recommended.

Category: Benign

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

In most follow-up studies of breast FNAB a histological diagnosis was not required after a benign FNAB diagnosis to determine the NPV and PPV of the benign category. A benign FNAB diagnosis with negative clinical and imaging findings is regarded as sufficient diagnostic work up, and if still negative at 6–12 months the benign FNAB is regarded as correct. The ROM is reported as in the range of 1–3% [14, 15, 44–46]. Two recent studies reported an NPV of a benign FNAB with histopathological follow-up as ranging from 97.1 to 98.97% [16, 17].

Because the vast majority of benign FNAB do not proceed to histopathological biopsy, an "overall" sensitivity for benign cytology can be calculated from the total number of FNAB in a series as "the number of correctly identified benign lesions," "expressed as a percentage of the total number of benign FNAB diagnoses" [47]. This was calculated in a recent study as 96.9% and reflects the sensitivity of benign breast FNAB in practice [17]. Rates of benign diagnoses vary between different practices, for instance between mammographic screening program assessment clinics and a breast clinic for patients presenting with breast lumps or pain [17].

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 [11, 13]. Although rarely sampled, normal breast tissue yields intact lobules and small terminal ductular tissue fragments showing ductal nuclei and myoepithelial nuclei. (Fig. 1) The nuclei of terminal ductules and ductal epithelium vary in size and chromatin pattern from small and fine, in normal epithelial components, to moderately large and mildly coarse in proliferative lesions, while nucleoli vary from small and inconspicuous to single larger round nucleoli [11, 13, 48].

The most common benign lesions diagnosed by FNAB include: *acute mastitis* and *breast abscess; granulomatous mastitis* due to specific infections, including tuberculosis [49] and nonspecific inflammatory processes that require microbiological studies, including culture or molecular testing to exclude tuberculosis; *foreign body reactions* such as that to silicone [50]; *fat necrosis; cysts* with apocrine sheets in a proteinaceous background (Fig. 2); material *"consistent with cyst contents"* when there is a granular proteinaceous background with no epithelium and there is correlation with imaging and clinical findings and the cyst completely drained; *fibrocystic change* with apocrine sheets and small cohesive ductal epithelial tissue fragments in a proteinaceous background (Fig. 3); *lactational change* with small acinar sheets of vacuolated cells and stripped acinar nuclei in a milky proteinaceous background including fine fat globules; *normal breast* with lobules and small terminal ductular tissue fragments in a clean background with bare bipolar nuclei (Fig. 1); *usual epithelial hyperplasia* with cohesive large ductal epithelial tissue fragments with myoepithelial cells and with bare

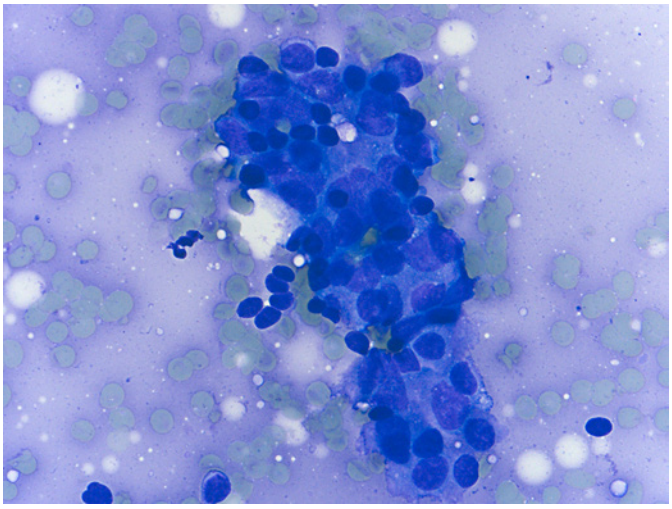

Fig. 1. Normal breast tissue, small terminal ductule: small epithelial tissue fragment showing larger ductal nuclei with bland chromatin and smaller oval darker myoepithelial nuclei; bare bipolar oval nuclei in the background (Giemsa, ×400).

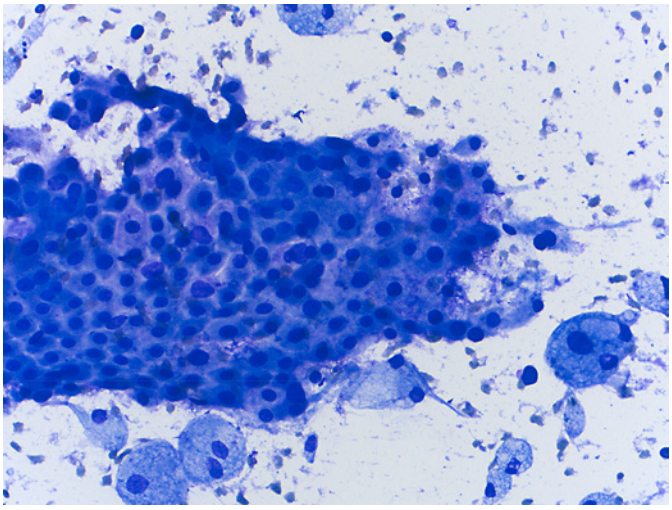

Fig. 2. Cyst: sheet of metaplastic apocrine cells and histiocytes and multinucleated histiocytes in a proteinaceous background (Giemsa, ×200).

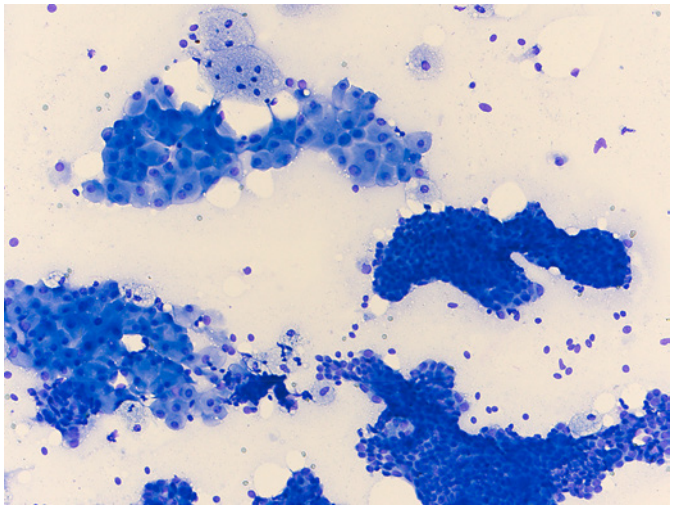

Fig. 3. Fibrocystic change: sheets of metaplastic apocrine cells, slightly enlarged cohesive tissue fragments of ductal epithelial cells with small, oval and dark myoepithelial nuclei, oval bare bipolar nuclei and some histiocytes and multinucleated histiocytes in a thin proteinaceous background (Giemsa, ×100).

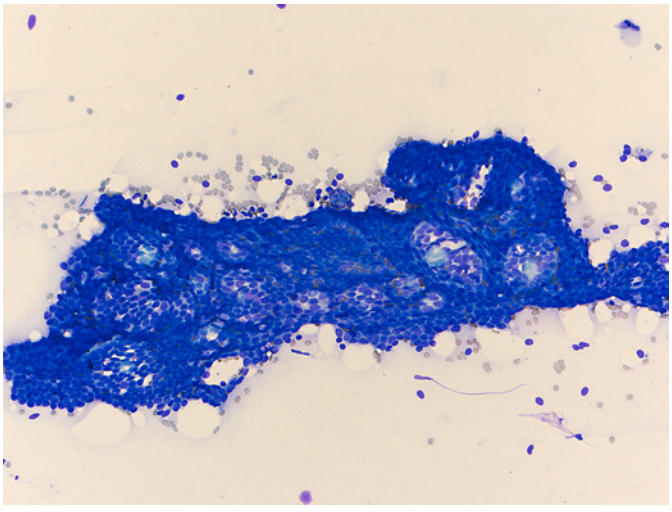

Fig. 4. Epithelial hyperplasia: large cohesive irregular ductal epithelial tissue fragment with slit-like secondary lumina and dark oval myoepithelial nuclei in a clean background with oval bare bipolar nuclei (Giemsa, ×100).

bipolar nuclei in a clean background (Fig. 4); *fibroadenoma* with similar large ductal epithelial tissue fragments and plentiful bare bipolar nuclei and fibrillary or rounded stromal fragments (Fig. 5, 6); and *intraductal papilloma* with similar large ductal epithelial tissue fragments, along with papillary stellate and more complex meshwork fragments, apocrine sheets and siderophages in a proteinaceous background [51]. In male patients, *gynaecomastia* resembles epithelial hyperplasia with or without scanty stroma. *Intramammary lymph nodes* show a heterogeneous lymphoid population with predominantly small lymphocytes.

Cellularity is increased in the proliferative lesions such as usual epithelial hyperplasia and fibroadenomas, and is

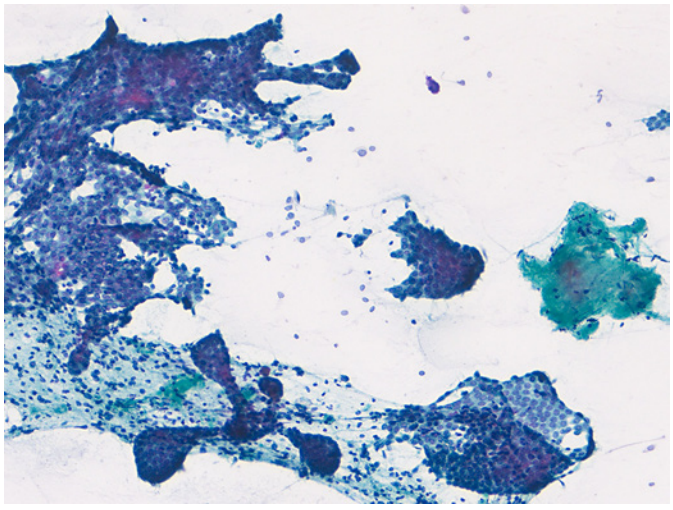

Fig. 5. Fibroadenoma: hyperplastic ductal epithelial tissue fragment with myoepithelial nuclei, branched dumb-bell ended epithelial tissue fragments, smaller epithelial tissue fragments, a folded ductal epithelial tissue fragment and a ragged fragment of stroma with some bare bipolar nuclei in the background (Pap, ×100).

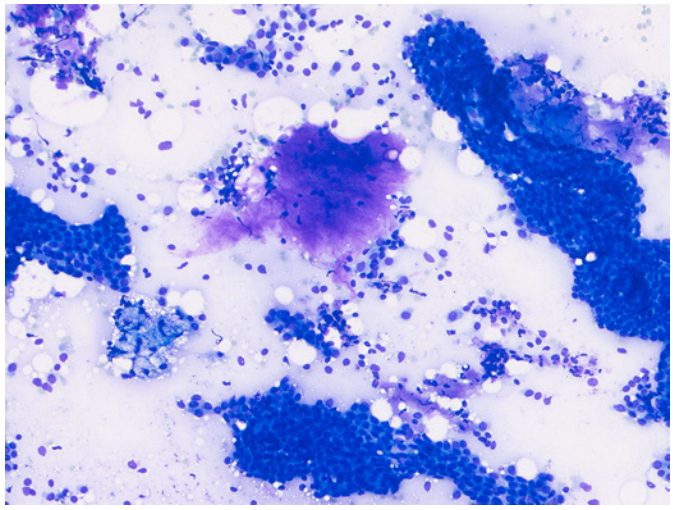

Fig. 6. Fibroadenoma: hyperplastic ductal epithelial tissue fragments, an irregular fragment of myxoid stroma and bare bipolar nuclei with some dispersed cells in the background; a small aggregate of histiocytes is also present (Giemsa, ×100).

often associated with increased dispersed single cells and admixed smaller tissue fragments with usually bland nuclei, while myoepithelial nuclei and bipolar nuclei are still present. If the overall pattern is diagnostic of a specific lesion such as a fibroadenoma, the high cellularity and dispersal and a degree of nuclear enlargement are still acceptable for a benign diagnosis [13]. The experience of the reporting cytopathologist will determine the threshold between a confident benign diagnosis and an atypical diagnosis in reporting these proliferative cases.

Management

For more than 50 years, FNAB of breast directed by palpation has provided an accurate diagnostic work up of breast lesions without necessarily any imaging, and this is particularly the case where clinical findings clearly correlate with the FNAB, for example, a cyst that completely drains with no palpable residual lesion, or a clinical abscess that yields purulent material, or a rounded mobile mass that has the characteristic cytological findings of a fibroadenoma, or a fixed gritty mass that has the findings of a carcinoma.

However, where imaging is available, best practice is to perform pre-FNAB imaging, utilize ultrasound or other imaging to direct the FNAB, and correlate the clinical, imaging and cytological findings in the triple test. The use of ultrasound guidance assists in ensuring the target lesion has been sampled. Correlation is essential and a benign FNAB diagnosis that correlates with the clinical and imaging findings does not require any further biopsy and no specific recommendation is needed in the report. However, if the clinical or imaging assessment is indeterminate and not explained by the cytology, or if it is suspicious, the cytology should be reported as benign, and follow-up biopsy usually by CNB should be recommended. Conversely, indeterminate cases on imaging, such as an apparent fibroadenoma that may have some irregularities, when reported as benign on FNAB do not require further work up.

Follow-up for a benign FNAB diagnosis varies with the nature of the benign lesion, for example, follow-up for an abscess may be after 2 weeks of antibiotics. Follow-up also varies between institutions and countries, but it is usually at 12–24 months, with the patient returned to routine screening in mammographic screening programs.

Category: Atypical

Definition: The term atypical in breast FNAB cytology 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.

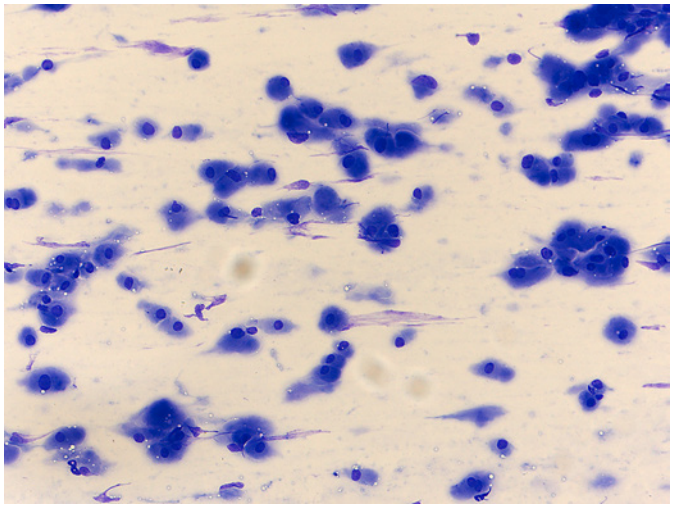

Fig. 7. Dispersed cells with mildly variable nuclei could be regarded as atypical, but they are apocrine cells with a low N:C ratio with evidence of crush artefact in the chromatinic smearing (Giemsa, ×100).

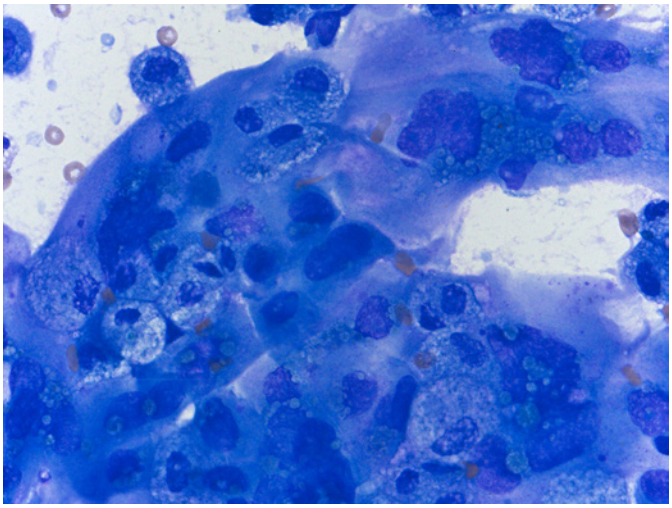

Fig. 8. Epithelial sheet showing nuclear variation in size, chromatin and shape, multinucleation and infiltrating histiocytes, could be regarded as atypical; but a low N:C ratio, apocrine cytoplasmic differentiation, histiocytes and a proteinaceous background are present (Giemsa, ×400).

The ROM of an atypical diagnosis varies in the literature from 22 to 39% [10, 14, 52–57], reflecting the variability of the definition and usage of the term "atypical" in the literature. Two more recent studies that looked at applying the IAC Yokohama System had ROM of 13 and 15.7% [16, 17]. As the body of literature regarding the System grows, the ROM of an atypical cytologic diagnosis will be refined.

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 [11, 13]. The diagnosis, if possible, should include the differential diagnosis and the diagnosis considered most likely.

There are three major causes for "atypical" diagnoses on breast FNAB cytology, and in many cases these may all be contributing factors.

Firstly, the skill of the operator is most important [25, 35, 36]. Poor FNAB technique may result in low cellularity and obscuring blood or ultrasound gel, overly forceful smearing causing crush artefact and dispersal (Fig. 7), or poor handling of material, which results in air-drying artefact when there is a delay in immersing slides in alcohol for Papanicolaou-stained slides and slow drying artefact in wet slides intended for Giemsa-stained slides. All of these result in suboptimal smears making interpretation difficult.

Secondly, interpretative problems do occur, and are due to overlapping cytological features between proliferative breast lesions, such as usual epithelial hyperplasia, intraductal papillomas [58] and fibroadenomas [59], and low-grade in situ lesions and low-grade invasive carcinomas (Fig. 8) [11, 13, 60]. The specific diagnosis of low-grade ductal carcinoma in situ (LGDCIS) and lobular carcinoma in situ (LCIS) and the exclusion of invasive carcinoma in these cases is not possible in FNAB 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 [13]. CNB can be recommended.

Thirdly, the degree of training, experience, on-going case load and expertise of the cytopathologist in interpreting the material impact on atypical rates. Less experienced pathologists may focus on dispersal or nuclear atypia and ignore the overall diagnostic features of the lesion, most typically, a fibroadenoma [59–61].

Lesions commonly associated with an atypical diagnosis include usual epithelial hyperplasia by itself or associated with fibrocystic change, fibroadenomas [17, 59–61] (Fig. 9), radial scars [62] and intraductal papillomas [17, 59], and the much less common adenomyoepithelioma [63, 64] and spindle cell lesions [65]. The distinction between cellular fibroadenomas and low-grade phyllodes tumors based on stromal hypercellularity and stromal

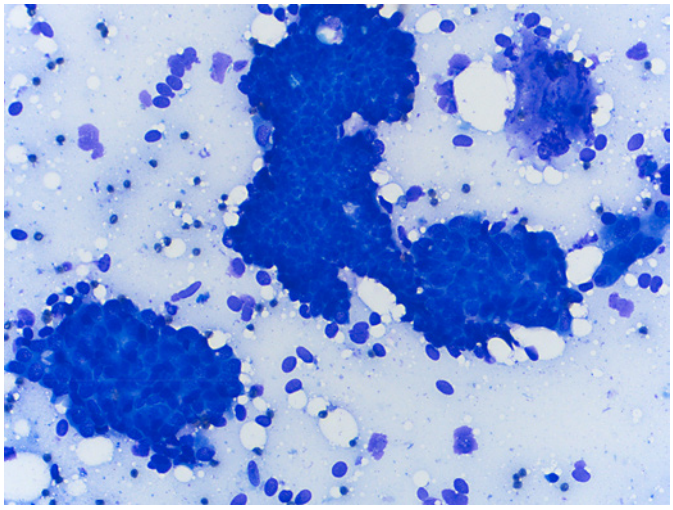

Fig. 9. Otherwise typical fibroadenoma with a (central) cohesive tissue fragment of ductal epithelial cells with myoepithelial cells, and two tissue fragments (right and bottom left) showing atypical crowding, nuclear overlapping and mild nuclear enlargement. Bare bipolar nuclei in the background (Giemsa, ×200).

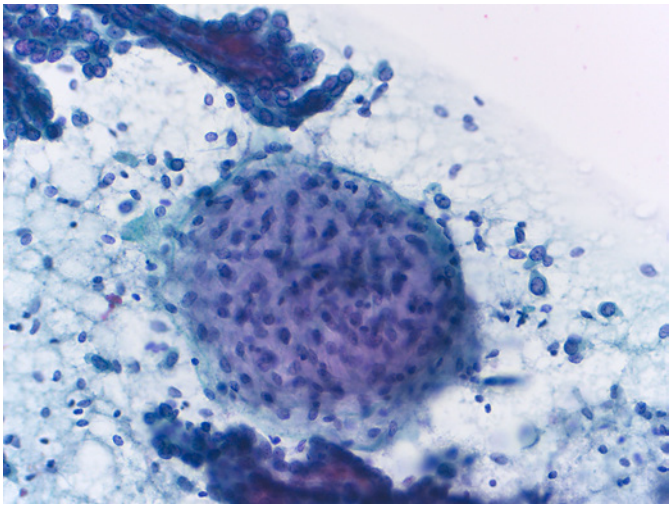

Fig. 10. Atypical stromal fragment showing mild hypercellularity and mild nuclear enlargement and atypia with two ductal epithelial tissue fragments and occasional spindle stromal cells in the background, raising the possibility of a low-grade phyllodes tumor (Pap, ×200).

atypia is problematic, as it is in CNB, due to the varying cellularity, atypia and mitotic counts in each phyllodes tumors (Fig. 10) [66–69]. LCIS and invasive lobular carcinoma may both produce low cellularity and a dispersed pattern of small cells with mildly atypical nuclei, which can be difficult to distinguish from poorly sampled proliferative lesions such as fibroadenomas [11, 13, 16, 70]. The key to the correct diagnosis of proliferative and 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 [13].

Management

Repeat FNAB is recommended if the atypical diagnosis is considered primarily due to a technical problem. When there is sufficient quality material for interpretation, the triple test should be applied. If either or both the clinical and imaging findings are indeterminate or suspicious a repeat FNAB or, more commonly if available, CNB is mandatory. If neither clinical nor imaging findings are of concern, there is considerable variation in management dependent on the lesion and between breast care centers. The management options include to repeat the FNAB or to perform a CNB, or to review the patient with imaging at 3–6 months, with subsequent repeat FNAB or CNB if the lesion has changed. If imaging and CNB are not available, repeat FNAB and close follow-up are recommended.

Category: Suspicious of Malignancy

Definition: The term "suspicious of malignancy" in breast FNAB 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 definition and use of the term "suspicious of malignancy" varies in similar fashion to the term "atypical" and this is reflected in the published range of PPV of a suspicious diagnosis from 60 to 95% [3–6, 8, 12, 14, 15, 70–78]. Two recent studies utilizing the IAC Yokohama System had ROM for a "suspicious of malignancy" diagnosis of 97.1 and 84.6% [16, 17]. The inclusion of a suspicious category helps maintain the high PPV of a malignant diagnosis while maintaining the sensitivity of FNAB cytology. The causes of a "suspicious of malignancy" diagnosis are similar to those of the atypical category and include technical problems related to the skill of the operator performing the FNAB, making smears and handling the material, the experience of the interpreting cytopathologist, and the nature of the breast lesion (Fig. 11, 12).

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 [13, 79]. This mirrors the difficulties in surgical

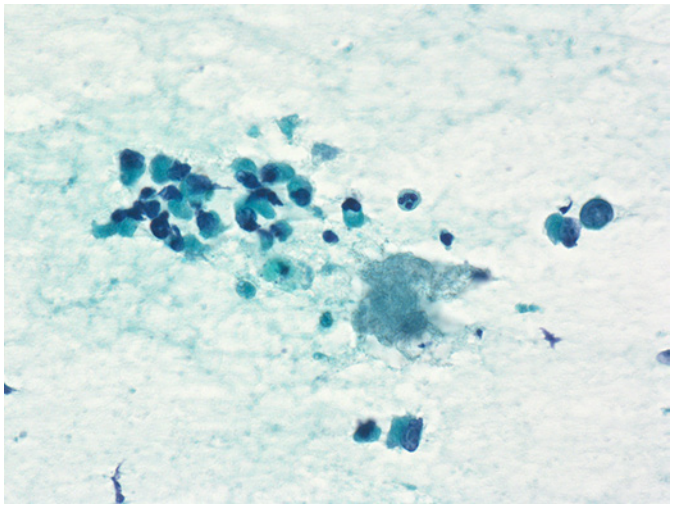

Fig. 11. Dispersed single cells showing eccentric cytoplasm and hyperchromatic, moderately pleomorphic nuclei with considerable smearing artefact and blurring of chromatin, "suspicious of malignancy" (Pap, ×200).

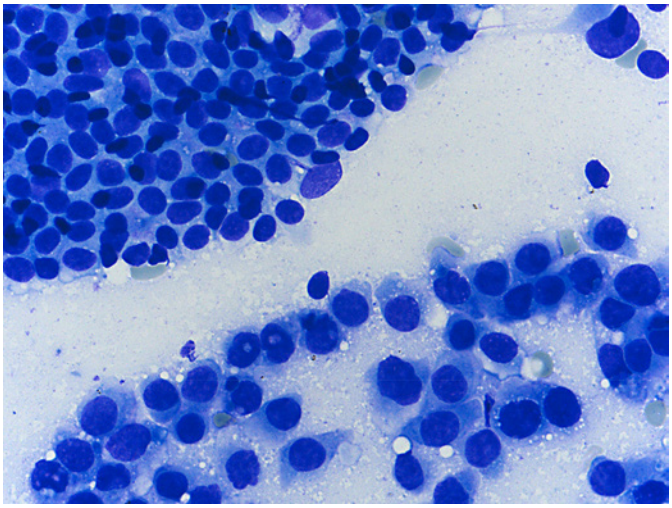

Fig. 12. Dispersed single intact cells with large hyperchromatic pleomorphic nuclei and occasional prominent nucleoli, juxtaposed to a ductal epithelial tissue fragment (upper) with regular ductal nuclei and plentiful oval dark myoepithelial nuclei: the decision to call this lesion "carcinoma" or to categorize it "suspicious of malignancy," because of the presence of a benign component, will depend on the amount of malignant material and the confidence of the reporting cytopathologist (Giemsa, ×400).

pathology in distinguishing atypical proliferative lesions from LGDCIS [80].

LGDCIS includes a range of solid, cribriform, micropapillary, papillary and solid papillary subtypes, and although rarely producing a clinical or radiological mass it may be associated with microcalcifications. In surgical pathology, LGDCIS is often an incidental finding in association with both benign and malignant lesions, or a lesion that is found in the work up of mammographic calcifications [80]. FNAB cytology cannot specifically diagnose LGDCIS and at the same time exclude invasive carcinoma [79, 81, 82].

In FNAB cytology, LGDCIS most typically produces 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 (Fig. 13, 14) [11, 13, 81–83].

Recognition of these features prevents under-calling LGDCIS as a proliferative lesion, and over-calling LGDCIS as invasive carcinoma [60, 79]. Although controversial in relation to the specific diagnosis of LGDCIS, the categorization of these lesions as "suspicious of malignancy" is recommended. Correlation with imaging is required, utilizing the triple test approach, and a more specific diagnosis in both cytology and imaging refines the triple test approach.

The diagnosis of high-grade ductal carcinoma in situ (HGDCIS) by FNAB is also controversial [83–86]. FNAB cannot diagnose HGDCIS to the exclusion of invasive carcinoma. HGDCIS is often associated with casting pleomorphic calcifications on mammography, and occasionally may produce a palpable or imaging mass lesion in the absence of invasive carcinoma [80].

In FNAB cytology smears, HGDCIS 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 [87]. The smears are often low in cellularity reflecting the small volume of cancer cells in ducts relative to breast tissue [87]. These findings cannot exclude high-grade invasive carcinomas, particularly those of no special type and metaplastic carcinomas, which can also show necrosis. It is highly debated as to whether "suggesting that there is an HGDCIS component" assists management.

Few institutions and cytopathologists have attempted to diagnose the presence of HGDCIS "with or without an invasive component" or to use the "suspicious of malig-

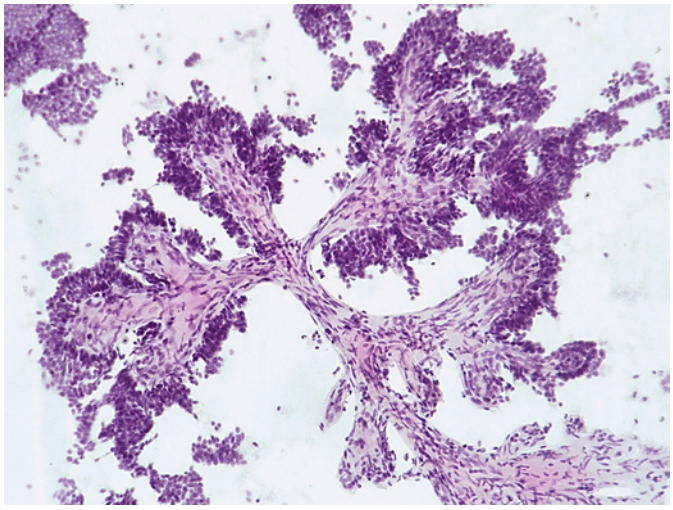

Fig. 13. Papillary tissue fragment consisting of thin fibrovascular branching stroma, covered in crowded epithelium, suggesting a papillary intraductal carcinoma in situ; the suggested categorization is "suspicious of malignancy" (Pap, ×100).

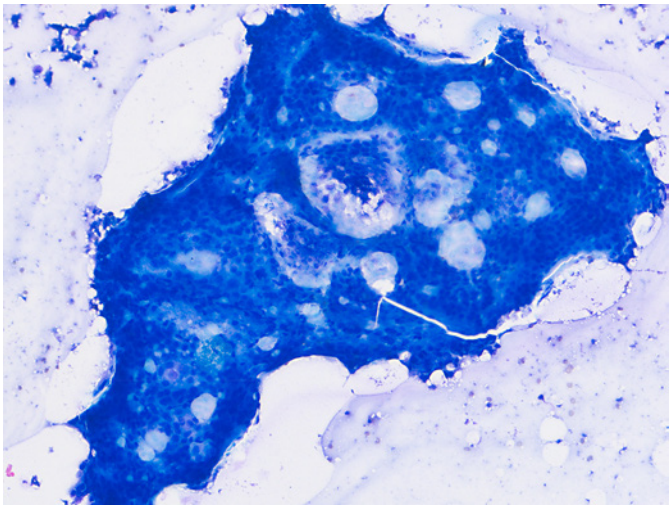

Fig. 14. Large epithelial tissue fragment showing a cribriform architecture, with crowded cells, mild nuclear pleomorphism and a tendency for the nuclei to orientate to the luminal spaces rather than stream, suggesting cribriform intraductal carcinoma; the suggested categorization is "suspicious of malignancy" (Giemsa, ×100).

nancy" category for these cases. In the past an outright malignant breast FNAB could lead to a full axillary clearance only to find just HGDCIS in the mastectomy. Currently, axillary dissection at the time of resection of the breast primary is guided by sentinel lymph node biopsy or a prior positive FNAB or CNB of axillary lymph nodes [88]. Furthermore, the use of sentinel lymph node biopsy and surgical management of HGDCIS and invasive carcinoma are similar in many institutions.

A highly dispersed pattern of large atypical cells may also raise the differential diagnosis of lymphoma, and a "suspicious of malignancy" categorization may be prudent to avoid unnecessary surgery. If lymphoma is suspected based on ROSE, material may be triaged for flow cytometry if available and/or cell block for immunohistochemistry.

Management

A "suspicious of malignancy" FNAB cytology diagnosis should lead to review of the imaging findings, but further biopsy is an absolute requirement and most commonly this will be a CNB. If CNB is not available, then surgical excision biopsy is required before specific treatment in almost all cases. When the "suspicious of malignancy" diagnosis is made at ROSE, immediate CNB is ideal.

Category: Malignant

Definition: A malignant cytological diagnosis is an unequivocal statement that the material is malignant, and the type of malignancy identified should be stated whenever possible.

The PPV of a malignant breast FNAB ideally should be 100%, but there is a reported range from 92 to 100% [3–6, 8, 12, 14, 15, 70–78]. Two recent studies utilizing the IAC Yokohama Reporting System had ROM of 100 and 99.0% for the malignant category [16, 17].

The malignant diagnosis should only be used when there is a full constellation of cytological findings and no discrepant features. These 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 (Fig. 15) [11, 13]. The nuclear features of malignancy will vary from low- to high-grade carcinomas, and none of these features taken separately is pathognomonic of carcinoma.

Various other cytological features have been suggested as evidence of invasive carcinoma, including tubular architecture of epithelial fragments, intracytoplasmic lumina in atypical epithelial cells and elastoid fragments [86, 89, 90]. The presence of stromal fragments infiltrated by

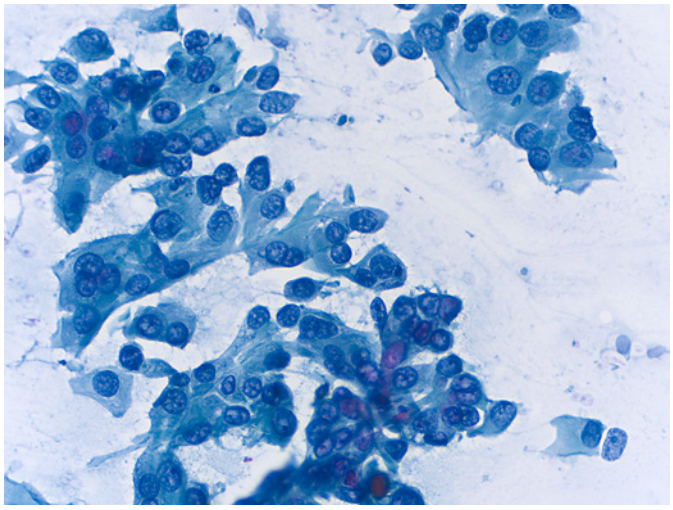

Fig. 15. Carcinoma in fraying, discohesive tissue fragments with high-grade, enlarged pleomorphic nuclei showing irregular granular chromatin and nucleoli, a variable but often high N:C ratio and a suggestion of gland formation (upper right). Carcinoma of no specific type on histopathology (Pap, ×200).

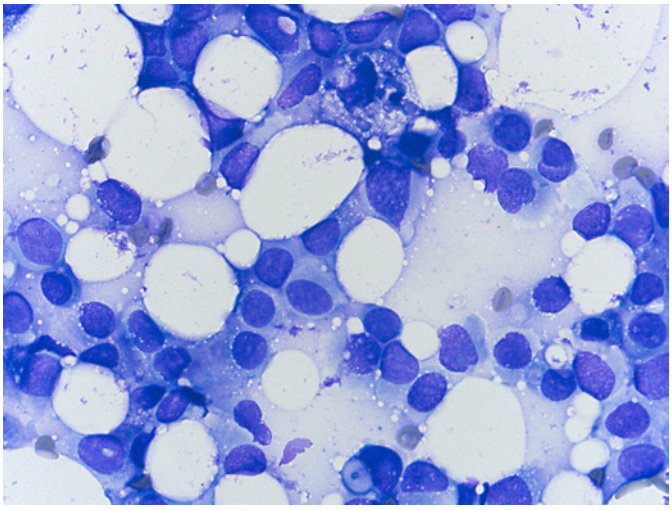

Fig. 16. Carcinoma with intermediate-sized cells, mildly enlarged, mildly pleomorphic nuclei (note the comparison in size to the macrophage nucleus, top center) and eccentric cytoplasm containing an occasional vacuole in some cells. Lobular carcinoma on histopathology (Giemsa, ×400).

carcinoma in breast smears resembling smaller fragments seen in CNB is regarded by some authors as being categorical evidence of invasive carcinoma [13, 91].

It is recommended that the type of malignancy should be mentioned or at least suggested in the report. It is recognized that this is not always possible, and lesions such as pleomorphic lobular carcinoma are not distinguishable reliably from high-grade invasive carcinoma, no special type [13].

The most common types of carcinoma which can be suggested in breast FNAB cytology based on their cytological characteristics are no special type (ductal) (Fig. 15), lobular (Fig. 16), mucinous (Fig. 17) [92], tubular and metaplastic. Ancillary studies such as E-cadherin for lobular carcinoma can be applied to cell blocks [11, 13, 29, 91] or liquid-based cytology [28, 93]. Less common carcinomas that might be suggested or diagnosable based on their key cytological features with or without ancillary studies are carcinoma with medullary features, adenoid cystic carcinoma, carcinoma with apocrine differentiation, carcinoma with neuroendocrine features, and carcinoma with osteoclastic giant cells [94]. Also, malignant lymphomas, angiosarcomas and some metastatic carcinomas and metastatic melanoma to the breast can be diagnosed. Rare cases of secretory, histiocytoid, glycogen-rich and clear cell carcinoma have been reported in the cytological literature.

Management

A malignant FNAB cytology diagnosis should be correlated with the clinical and imaging findings, and if the triple test is concordant and material is available in the cell block for prognostic and treatment markers [29], definitive therapy including neoadjuvant chemotherapy and surgery can be commenced. Some centers will proceed on the basis of a positive triple test to surgical excision with the markers being performed on the excised lesion. However, many centers and treatment and trial protocols in the developed world require CNB before neo-adjuvant chemotherapy or definitive surgery.

If the FNAB cytology diagnosis does not correlate with the other components of the triple test, CNB or, if this is not available, simple excision biopsy, is mandatory prior to commencing definitive treatment.

If the axillary lymph nodes are palpable or enlarged or suspicious on ultrasound of the axilla, FNAB is recommended to stage the patient who has presented with a breast lesion. Some centers will then proceed to CNB of the lymph node to confirm the FNAB findings. Other centres may use only CNB to assess the lymph node, possibly because ROSE at the time of a FNAB is not available [88]. If the lymph node cytology shows metastatic carcinoma the patient is staged. If the lymph node cytology is negative or suspicious of metastatic carcinoma then sentinel lymph node biopsy is required.

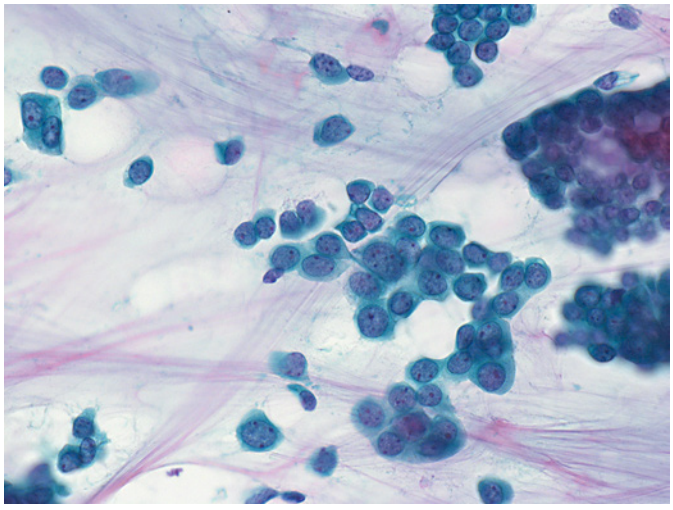

Fig. 17. Dispersed single cells and discohesive small tissue fragments of intermediate-sized cells with a high N:C ratio and moderately enlarged and mildly pleomorphic nuclei with small nucleoli, in a fibrillary mucinous background. Mucinous carcinoma on histopathology (Pap, ×400).

Ancillary Techniques

Independent of the preparation used, FNAB of breast cytology provides good and reliable material for ancillary studies [93]. This material can be found in direct smears fixed in alcohol with Papanicolaou or HE staining or air dried and stained with a Giemsa or similar stain, as well as, in liquid-based cytology preparations and formalin-fixed paraffin-embedded cell blocks. The ancillary studies include immunocytochemistry, immunohistochemistry and molecular techniques. These ancillary techniques are of value in specific situations that include: diagnostic difficulties, for example, utilizing myoepithelial cell markers on cell block material in atypical and suspicious lesions; immunohistochemistry on cell blocks for the prognostic and predictive markers for estrogen, progesterone and HER2 receptors; in situ hybridization for HER2 on cell blocks; immunohistochemistry for the determination of a primary site in metastatic lesions; and the study of prognostic and predictive markers in the metastatic breast cancer setting [12, 25, 93].

In some centers around the world, patients are treated preoperatively with neo-adjuvant chemotherapy on the basis of the FNAB in the context of the triple test, without a CNB or surgical biopsy. The FNAB smears and cell block can provide material for predictive markers [25]. Tracking breast cancer evolution by using high-throughput technology such as next-generation sequencing to detect ER or HER2 mutations using FNAB material from breast cancer metastases is one of the next developments in the changing world of the application of molecular testing in FNAB of the breast.

Conclusion

The IAC Yokohama System for Reporting Breast FNAB cytology defines five categories for reporting breast cytology and this article provides discussion on the use of these categories. The categories effectively stratify breast lesions by their ROM and provide guidance within a management algorithm for each category [1]. Each category has a specific recommended term and in the case of inadequate/insufficient a choice of two terms. The System emphasizes the crucial importance of high-quality performance of the FNAB procedure and of the making of direct smears. The interpretation of the smears also requires good training and on-going experience, and the authors believe will be greatly helped by the forthcoming Atlas.

The authors recognize that the performance indicators of breast FNAB, including specificity and sensitivity, NPV, PPV and ROM stated in this article are those derived from reviews of the literature and recent articles. It is hoped that the Reporting System will stimulate research into these indicators to test the current System and its management recommendations. The authors also recognize that reviews of past studies, which vary in patient population, diagnostic approach and statistical analysis, may not represent current best practice, which now includes sophisticated imaging and in many patients the use of ultrasound to assist with guidance of the FNAB and the use of ROSE. ROSE provides the opportunity to immediately assess the FNAB material for adequacy and triage the case for the most cost-effective further diagnostic procedures including immediate CNB [17, 95]. When a cytopathologist has made the provisional diagnosis at ROSE this can guide discussion with the patient, greatly reducing patient anxiety [96].

The management recommendations provide options because the authors recognize that there are variations internationally and within countries in the application and the use of FNAB and CNB. The availability of imaging and CNB with its inherent need for readily available histopathology laboratories vary between those countries with well-developed medical infrastructure and those low- and middle-income countries with more limited resources [97]. The use of FNAB and CNB will also

vary with the availability of expertise and the clinical practice.

Finally, the IAC Yokohama System will invoke a response from the cytology community and also from all those who provide a component in the "triple" diagnostic approach, which is the best practice for women with breast lesions. The authors sincerely hope that this will lead to better patient care.

Disclosure Statement

This System for Reporting Breast FNAB Cytology has been developed under the auspices of the IAC. No funding was received. The authors have no conflicts of interest to declare. All authors contributed to the writing and editing of this manuscript.

References

1 Field AS, Vielh P, Schmitt F. IAC Standardized Reporting of Breast FNA Biopsy Cytology. Acta Cytol. 2017;61:3–6.
2 National Cancer Institute Fine-Needle Aspiration of Breast Workshop Subcommittees. The Uniform Approach to Breast Fine-Needle Aspiration Biopsy. Diagn Cytopathol. 1997;16(4):295–311.
3 Nguansangiam S, Jesdapatarakul S, Tangjitgamol S. Accuracy of fine needle aspiration cytology from breast masses in Thailand. Asian Pac J Cancer Prev. 2009 Oct-Dec;10(4):623–6.
4 Abdel-Hadi M, Abdel-Hamid GF, Abdel-Razek N, Fawzy RK. Should fine-needle aspiration cytology be the first choice diagnostic modality for assessment of all nonpalpable breast lesions? The experience of a breast cancer screening center in Alexandria, Egypt. Diagn Cytopathol. 2010 Dec;38(12):880–9.
5 Aker F, Gümrükçü G, Onomay BC, Erkan M, Gürleyik G, Kiliçoğlu G, et al. Accuracy of fine-needle aspiration cytology in the diagnosis of breast cancer a single-center retrospective study from Turkey with cytohistological correlation in 733 cases. Diagn Cytopathol. 2015 Dec;43(12):978–86.
6 Daramola AO, Odubanjo MO, Obiajulu FJ, Ikeri NZ, Banjo AA. Correlation between fine-needle aspiration cytology and histology for palpable breast masses in a Nigerian tertiary health institution. Int J Breast Cancer. 2015;2015:742573.
7 Nkonge KM, Rogena EA, Walong EO, Nkonge DK. Cytological evaluation of breast lesions in symptomatic patients presenting to Kenyatta National Hospital, Kenya: a retrospective study. BMC Womens Health. 2015 Dec;15(1):118.
8 Mišković J, Zorić A, Radić Mišković H, Šoljić V. Diagnostic Value of Fine Needle Aspiration Cytology for Breast Tumors. Acta Clin Croat. 2016 Dec;55(4):625–8.
9 Ibikunle DE, Omotayo JA, Ariyibi OO. Fine needle aspiration cytology of breast lumps with histopathologic correlation in Owo, Ondo State, Nigeria: a five-year review. Ghana Med J. 2017 Mar;51(1):1–5.
10 Yu YH, Wei W, Liu JL. Diagnostic value of fine-needle aspiration biopsy for breast mass: a systematic review and meta-analysis. BMC Cancer. 2012 Jan;12(1):41–60.
11 Ducatman BS, Wang HH. Breast. In: Cibas E, Ducatman B, editors. Cytology: principles and clinical correlates, 4th ed. Amsterdam: Elsevier; 2014.
12 Dong J, Ly A, Arpin R, Ahmed Q, Brachtel E. Breast fine needle aspiration continues to be relevant in a large academic medical center: experience from Massachusetts General Hospital. Breast Cancer Res Treat. 2016 Jul;158(2):297–305.
13 Field AS. Chapter 5, Fine needle aspiration biopsy cytology of breast: a diagnostic approach based on pattern recognition'. In: Practical Cytopathology: a Diagnostic Approach to Fine Needle Aspiration Biopsy'. Edited by Field AS and Zarka MR. Amsterdam: Elsevier; 2017.
14 Wang M, He X, Chang Y, Sun G, Thabane L. A sensitivity and specificity comparison of fine needle aspiration cytology and core needle biopsy in evaluation of suspicious breast lesions: a systematic review and meta-analysis. Breast. 2017 Feb;31:157–66.
15 Hoda RS, Arpin Iii RN, Gottumukkala RV, Hughes KS, Ly A, Brachtel EF. Diagnostic value of fine-needle aspiration in male breast lesions. Acta Cytol. 2019. doi: 10.1159/000494486.
16 Montezuma D, Malheiros D, Schmitt F. Breast FNAB cytology using the newly proposed IAC Yokohama System for Reporting Breast Cytopathology: the experience of a single institution. Acta Cytol. 2019. doi: 10.1159/000492638.
17 Wong S, Rickard M, Earls P, Arnold L, Bako B, Field AS. The IAC Yokohama System for reporting breast FNAB cytology: a single institutional retrospective study of the application of the system and the impact of ROSE. Acta Cytol. 2019. doi: 10.1159/0005001991.
18 Boerner S, Sneige N. Specimen adequacy and false-negative diagnosis rate in fine-needle aspirates of palpable breast masses. Cancer. 1998 Dec;84(6):344–8.
19 Bulgaresi P, Cariaggi P, Ciatto S, Houssami N. Positive predictive value of breast fine-needle aspiration cytology (FNAC) in combination with clinical and imaging findings: a series of 2334 subjects with abnormal cytology. Breast Cancer Res Treat. 2006;97(3):319–21.
20 Field AS. Breast FNAB cytology: current problems and the International Academy of Cytology Yokohama Standardized Reporting System. Cancer Cytopathol. 2017;125(4):229–30.
21 Masood S, Rosa M, Kraemer DF, Smotherman MS, Mohammadi A. Comparative cost-effectiveness of FNAB versus image-guided CNB, and open surgical biopsy in the evaluation of breast cancer in the era of the Affordable Care Act: a changing landscape. Diagn Cytopathol. 2015;43(8):605–12.
22 van Zante A, Ljung BM. Fine-needle aspiration versus core needle biopsy: reconsidering the evidence of superiority. Cancer Cytopathol. 2016 Dec;124(12):853–6.
23 Uematsu T, Kasami M. Risk of needle tract seeding of breast cancer: cytological results derived from core wash material. Breast Cancer Res Treat. 2008 Jul;110(1):51–5.
24 Sennerstam RB, Franzén BS, Wiksell HO, Auer GU. Core-needle biopsy of breast cancer is associated with a higher rate of distant metastases 5 to 15 years after diagnosis than FNA biopsy. Cancer Cytopathol. 2017 Oct;125(10):748–56.
25 Ljung BM, Drejet A, Chiampi N, et al. Diagnostic accuracy of fine-needle aspiration biopsy is determined by physician training in sampling technique. Cancer. 2001;93(4):263–8.
26 Brown LA, Coghill SB. Fine needle aspiration cytology of the breast: factors affecting sensitivity. Cytopathology. 1991;2(2):67–74.
27 Howell LP, Gandour-Edwards R, Folkins K, Davis R, Yasmeen S, Afify A. Adequacy evaluation of fine-needle aspiration biopsy in the breast health clinic setting [cytopathol]. Cancer. 2004 Oct;102(5):295–301.
28 Gerhard R, Schmitt FC. Liquid-based cytology in fine-needle aspiration of breast lesions: a review. Acta Cytol. 2014;58(6):533–42.

29 Vohra P, Buelow B, Chen YY, Serrano M, Vohra MS, Berry A, et al. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer FNA cell blocks and paired histologic specimens: A large retrospective study. Cancer Cytopathol. 2016 Nov;124(11):828–35.
30 Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017 Nov;27(11):1341–6.
31 Layfield LJ, Mooney EE, Glasgow B, Hirschowitz S, Coogan A. What constitutes an adequate smear in fine-needle aspiration cytology of the breast? Cancer. 1997 Feb;81(1):16–21.
32 Rubenchik I, Sneige N, Edeiken B, Samuels B, Fornage B. In search of specimen adequacy in fine-needle aspirates of nonpalpable breast lesions. Am J Clin Pathol. 1997 Jul;108(1):13–8.
33 Park IA, Ham EK. Fine needle aspiration cytology of palpable breast lesions. Histologic subtype in false negative cases. Acta Cytol. 1997 Jul-Aug;41(4):1131–8.
34 Pisano ED, Fajardo LL, Caudry DJ, Sneige N, Frable WJ, Berg WA, et al. Fine-needle aspiration biopsy of nonpalpable breast lesions in a multicenter clinical trial: results from the radiologic diagnostic oncology group V. Radiology. 2001 Jun;219(3):785–92.
35 Lee KR, Foster RS, Papillo JL. Fine needle aspiration of the breast. Importance of the aspirator. Acta Cytol. 1987 May-Jun;31(3):281–4.
36 Barrows GH, Anderson TJ, Lamb JL, Dixon JM. Fine-needle aspiration of breast cancer. Relationship of clinical factors to cytology results in 689 primary malignancies. Cancer. 1986 Oct;58(7):1493–8.
37 Palombini L, Fulciniti F, Vetrani A, De Rosa G, Di Benedetto G, Zeppa P, et al. Fine-needle aspiration biopsies of breast masses. A critical analysis of 1956 cases in 8 years (1976-1984). Cancer. 1988 Jun;61(11):2273–7.
38 Ciatto S, Cariaggi PP, Bulgaresi P, Confortini M, Bonardi R. Fine needle aspiration cytology of the breast: review of 9533 consecutive cases. Breast. 1993;2(2):87–90.
39 Snead DR, Vryenhoef P, Pinder SE, Evans A, Wilson AR, Blamey RW, et al. Routine audit of breast fine needle aspiration (FNA) cytology specimens and aspirator inadequate rates. Cytopathology. 1997 Aug;8(4):236–47.
40 Patel JJ, Gartell PC, Smallwood JA, Herbert A, Royle G, Buchanan R, et al. Fine needle aspiration cytology of breast masses: an evaluation of its accuracy and reasons for diagnostic failure. Ann R Coll Surg Engl. 1987 Jul;69(4):156–9.
41 Feichter GE, Haberthür F, Gobat S, Dalquen P. Breast cytology. Statistical analysis and cytohistologic correlations. Acta Cytol. 1997 Mar-Apr;41(2):327–32.
42 Lieske B, Ravichandran D, Wright D. Role of fine-needle aspiration cytology and core biopsy in the preoperative diagnosis of screen-detected breast carcinoma. Br J Cancer. 2006 Jul;95(1):62–6.
43 Pennes DR, Naylor B, Rebner M. Fine needle aspiration biopsy of the breast. Influence of the number of passes and the sample size on the diagnostic yield. Acta Cytol. 1990 Sep-Oct;34(5):673–6.
44 O'Neill S, Castelli M, Gattuso P, Kluskens L, Madsen K, Aranha G. Fine-needle aspiration of 697 palpable breast lesions with histopathologic correlation. Surgery. 1997;122:824–828.
45 Boerner S, Fornage BD, Singletary E, Sneige N. Ultrasound-guided fine-needle aspiration (FNA) of nonpalpable breast lesions: a review of 1885 FNA cases using the National Cancer Institute-supported recommendations on the uniform approach to breast FNA. Cancer. 1999 Feb;87(1):19–24.
46 Day C, Moatamed N, Fimbres AM, Salami N, Lim S, Apple SK. A retrospective study of the diagnostic accuracy of fine-needle aspiration for breast lesions and implications for future use. Diagn Cytopathol. 2008 Dec;36(12):855–60.
47 Singh N, Wells CA. Assessment of accuracy in breast cytology. Cytopathology. 2001 Aug;12(4):211–8.
48 Kashyap A, Jain M, Shukla S, Andley M. Study of nuclear morphometry on cytology specimens of benign and malignant breast lesions: A study of 122 cases. J Cytol. 2017 Jan-Mar;34(1):10–5.
49 Tandom M, Chintamami, Panwar P. Breast tuberculosis at a teaching care centre: a retrospective analysis of 22 cases. Breast Dis. 2014;34(3):127–30.
50 Santos-Briz A Jr, López-Ríos F, Santos-Briz A, De Agustín PP. Granulomatous reaction to silicone in axillary lymph nodes. A case report with cytologic findings. Acta Cytol. 1999 Nov-Dec;43(6):1163–5.
51 Field A, Mak A. A prospective study of the diagnostic accuracy of cytological criteria in the FNAB diagnosis of breast papillomas. Diagn Cytopathol. 2007 Aug;35(8):465–75.
52 Ayata G, Abu-Jawdeh GM, Fraser JL, et al. Accuracy and consistency in application of a probabilistic approach to reporting breast fine needle aspiration. Acta Cytol. 2003;47(6):973–8.
53 Chaiwun B, Settakorn J, Ya-In C, Wisedmongkol W, Rangdaeng S, Thorner P. Effectiveness of fine-needle aspiration cytology of breast: analysis of 2,375 cases from northern Thailand. Diagn Cytopathol. 2002 Mar;26(3):201–5.
54 Goyal P, Sehgal S, Ghosh S, et al, Histopathological correlation of atypical (C3) and suspicious (C4) categories in FNA cytology of the breast. Int J Breast Cancer. 2013;2013:965498.
55 Weigner J, Zardawi I, Braye S, McElduff P. The microscopic complexities of C3 in breast cytology. Acta Cytol. 2014;58(4):335–46.
56 Arul P, Masilamani S, Akshatha C. Fine needle aspiration cytology of atypical (C3) and suspicious (C4) categories in the breast and its histopathologic correlation. J Cytol. 2016;33(2):76–9.
57 Yu SN, Li J, Wong SI, Tsang JY, Ni YB, Chen J, et al. Atypical aspirates of the breast: a dilemma in current cytology practice. J Clin Pathol. 2017 Dec;70(12):1024–32.
58 Field A, Mak A. The fine needle aspiration biopsy diagnostic criteria of proliferative breast lesions: a retrospective statistical analysis of criteria for papillomas and radial scar lesions. Diagn Cytopathol. 2007 Jul;35(7):386–97.
59 Simsir A, Waisman J, Cangiarella J. Fibroadenomas with atypia: causes of under- and overdiagnosis by aspiration biopsy. Diagn Cytopathol. 2001 Nov;25(5):278–84.
60 Bofin AM, Lydersen S, Hagmar BM. Cytological criteria for the diagnosis of intraductal hyperplasia, ductal carcinoma in situ, and invasive carcinoma of the breast. Diagn Cytopathol. 2004 Oct;31(4):207–15.
61 Deb RA, Matthews P, Elston CW, et al. An audit of 'equivocal' (C3) and suspicious (C4) categories in FNA cytology of breast. Cytopathology. 2001;1:219–26.
62 Orell SR. Radial scar/complex sclerosing lesion—a problem in the diagnostic work-up of screen-detected breast lesions. Cytopathology. 1999 Aug;10(4):250–8.
63 Vielh P, Thiery JP, Validire P, Annick de Maublanc M, Woto G. Adenomyoepithelioma of the breast: fine-needle sampling with histologic, immunohistologic, and electron microscopic analysis. Diagn Cytopathol. 1993;9(2):188–93.
64 Iyengar P, Ali SZ, Brogi E. Fine-needle aspiration cytology of mammary adenomyoepithelioma: a study of 12 patients. Cancer. 2006 Aug;108(4):250–6.
65 Chhieng DC, Cangiarella JF, Waisman J, Fernandez G, Cohen JM. Fine-needle aspiration cytology of spindle cell lesions of the breast. Cancer. 1999;87:359–71.
66 Bhattarai S, Kapila K, Verma K. Phyllodes tumor of the breast. A cytohistologic study of 80 cases. Acta Cytol. 2000 Sep-Oct;44(5):790–6.
67 Scolyer RA, McKenzie PR, Achmed D, Lee CS. Can phyllodes tumours of the breast be distinguished from fibroadenomas using fine needle aspiration cytology? Pathology. 2001 Nov;33(4):437–43.
68 Jayaram G, Sthaneshwar P. Fine-needle aspiration cytology of phyllodes tumors. Diagn Cytopathol. 2002 Apr;26(4):222–7.
69 Maritz RM, Michelow PM. Cytological criteria to distinguish phyllodes tumour of the breast from fibroadenoma. Acta Cytol. 2017;61(6):418–24.
70 Sneige N. Fine-needle aspiration of the breast: a review of 1,995 cases with emphasis on diagnostic pitfalls. Diagn Cytopathol. 1993;9(1):106–12.
71 O'Neil S, Castelli M, Gattuso P, Kluskens L, Madsen K, Aranha G. Fine-needle aspiration of 697 palpable breast lesions with histopathologic correlation. Surgery. 1997 Oct;122(4):824–8.

72 Zardawi IM, Hearnden F, Meyer P, Trevan B. Ultrasound-guided fine needle aspiration cytology of impalpable breast lesions in a rural setting. Comparison of cytology with imaging and final outcome. Acta Cytol. 1999 Mar-Apr; 43(2):163–8.
73 Westenend PJ, Sever AR, Beekman-De Volder HJ, Liem SJ. A comparison of aspiration cytology and core needle biopsy in the evaluation of breast lesions. Cancer. 2001 Apr;93(2):146–50.
74 Ariga R, Bloom K, Reddy VB, Kluskens L, Francescatti D, Dowlat K, et al. Fine-needle aspiration of clinically suspicious palpable breast masses with histopathologic correlation. Am J Surg. 2002 Nov;184(5):410–3.
75 Ishikawa T, Hamaguchi Y, Tanabe M, Momiyama N, Chishima T, Nakatani Y, et al. False-positive and false-negative cases of fine-needle aspiration cytology for palpable breast lesions. Breast Cancer. 2007;14(4):388–92.
76 Yamaguchi R, Tsuchiya SI, Koshikawa T, Ishihara A, Masuda S, Maeda I, et al. Diagnostic accuracy of fine-needle aspiration cytology of the breast in Japan: report from the Working Group on the Accuracy of Breast Fine-Needle Aspiration Cytology of the Japanese Society of Clinical Cytology. Oncol Rep. 2012 Nov;28(5):1606–12.
77 Rosa M, Mohammadi A, Masood S. The value of fine needle aspiration biopsy in the diagnosis and prognostic assessment of palpable breast lesions. Diagn Cytopathol. 2012 Jan; 40(1):26–34.
78 Farras Roca JA, Tardivon A, Thibault F, El Khoury C, Alran S, Fourchotte V, et al. Diagnostic Performance of Ultrasound-Guided Fine-Needle Aspiration of Nonpalpable Breast Lesions in a Multidisciplinary Setting: The Institut Curie's Experience. Am J Clin Pathol. 2017 Jun;147(6):571–9.
79 Silverman JF, Masood S, Ducatman BS, et al. Can FNA biopsy separate atypical hyperplasia, carcinoma in-situ, and invasive carcinoma of the breast? Cytomorphologic criteria and limitations in diagnosis. Diagn Cytopathol. 1993;24:630–5.
80 Lakhani EI Sr, Schnitt SJ, Tan PH, van de Vivjer M, editors. WHO classification of tumours of the breast. 4th ed. Lyon, IARC; 2012.
81 Bonzanini M, Gilioli E, Brancato B, Cristofori A, Bricolo D, Natale N, et al. The cytopathology of ductal carcinoma in situ of the breast. A detailed analysis of fine needle aspiration cytology of 58 cases compared with 101 invasive ductal carcinomas. Cytopathology. 2001 Apr;12(2):107–19.
82 Cangiarella J, Waisman J, Simsir A. Cytologic findings with histologic correlation in 43 cases of mammary intraductal adenocarcinoma diagnosed by aspiration biopsy. Acta Cytol. 2003 Nov-Dec;47(6):965–72.
83 Sauer T, Young K, Thoresen SO. Fine needle aspiration cytology in the work-up of mammographic and ultrasonographic findings in breast cancer screening: an attempt at differentiating in situ and invasive carcinoma [Thoresen SO, the 'O' is actually an O with a diagonal line. IF not available use Thoresen SE.]. Cytopathology. 2002 Apr;13(2):101–10.
84 Sauer T, Myrvold K, Lømo J, Anderssen KY, Skaane P. Fine-needle aspiration cytology in nonpalpable mammographic abnormalities in breast cancer screening: results from the breast cancer screening programme in Oslo 1996-2001. Breast. 2003 Oct;12(5):314–9.
85 Sauer T, Lømo J, Garred O, Naess O. Cytologic features of ductal carcinoma in situ in fine-needle aspiration of the breast mirror the histopathologic growth pattern heterogeneity and grading [Lomo is a small 'o' with a diagonal line, Garred is a capital 'O' with a diagonal line.]. Cancer. 2005 Feb;105(1):21–7.
86 Sauer T, Garred O, Lømo J, Naess O. Assessing invasion criteria in fine needle aspirates from breast carcinoma diagnosed as DICS or invasive carcinoma: can we identify an invasive component in addition to DCIS? [See Garred O as above.]. Acta Cytol. 2006 May-Jun;50(3):263–70.
87 Lilleng R, Hagmar B. The comedo subtype of intraductal carcinoma. Cytologic characteristics. Acta Cytol. 1992 May-Jun;36(3):345–52.
88 Gibbons CE, Quinn CM, Gibbons D. Fine Needle Aspiration Biopsy Management of the Axilla in Primary Breast Carcinoma. Acta Cytol. 2019. doi: 10.1159/000496159.
89 Bondeson L, Lindholm K. Prediction of invasiveness by aspiration cytology applied to nonpalpable breast carcinoma and tested in 300 cases. Diagn Cytopathol. 1997 Nov;17(5): 315–20.
90 Klijanienko J, Souer T, Garred U, et al. Assessing invasive criteria in FNA from breast carcinoma diagnosed as DCIS or invasive carcinoma: can we identify an invasive component in addition to DCIS? Acta Cytol. 2006;50z: 263–70.
91 Klijanienko J, Katsahian S, Vielh P, Masood S. Stromal infiltration as a predictor of tumor invasion in breast fine-needle aspiration biopsy. Diagn Cytopathol. 2004 Mar;30(3): 182–6.
92 Cyrta J, Andreiuolo F, Azoulay S, Balleyguier C, Bourgier C, Mazouni C, et al. Pure and mixed mucinous carcinoma of the breast: fine needle aspiration cytology findings and review of the literature. Cytopathology. 2013 Dec;24(6):377–84.
93 Beca F, Schmitt FS. Ancillary tests in breast FNAB cytology: a practical guide to current use. Acta Cytol. 2019. doi: 10.1159/000499697.
94 Jacquet SF, Balleyguier C, Garbay JR, Bourgier C, Mathieu MC, Delaloge S, et al. Fine-needle aspiration cytopathology – an accurate diagnostic modality in mammary carcinoma with osteoclast-like giant cells: a study of 8 consecutive cases. Cancer Cytopathol. 2010 Dec;118(6):468–73.
95 Delaloge S, Bonastre J, Borget I, Garbay JR, Fontenay R, Boinon D, et al. The challenge of rapid diagnosis in oncology: diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic. Eur J Cancer. 2016 Oct;66:131–7.
96 Boinon D, Dauchy S, Charles C, Fasse L, Cano A, Balleyguier C, et al. Patient satisfaction with a rapid diagnosis of suspicious breast lesions: association with distress and anxiety. Breast J. 2018 Mar;24(2):154–60.
97 Field AS. Cytopathology in Low Medical Infrastructure Countries: Why and How to Integrate to Capacitate Health Care. Clin Lab Med. 2018 Mar;38(1):175–82.