IAC Yokohama System for Reporting Breast FNAB Cytopathology

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IAC Tutorial
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Developing a System for Reporting Breast FNAB Cytopathology: How? Steps to Take

• Formed a steering committee of committed cytopathologists in breast FNAB: met in Yokohama at ICC, 2016
• Proposed system for categorization of breast FNAB: Acta Cytologica 2017
• Established editors and lead ‘chapter/topic’ authors and recruited writers for an atlas
• Literature search and writing of draft chapters, which circulated for review
• International web based survey based on the drafts. Dan Kurtycz at Wisconsin University in mid 2018. Edit drafts further.
• Summary article in Acta Cytologica
• Proposed system for categorization of breast FNAB: Acta Cytologica 2017
• Produce a comprehensive standardized approach to breast FNAB
• System will stimulate research assessing the system leading to improvements in patient care and revisions

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Field AS, Raymond W, Rickard M, and 22 authors
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Developing a System for Reporting Breast FNAB Cytopathology: so what is happening?

• IAC Yokohama System for Reporting Breast FNAB just e-published in May 2019
• Effusion Cytopathology in advanced development
• Lymph Node FNAB cytology about to publish a proposal
• Soft Tissue FNAB cytology preparing a proposal
• Lung Cytopathology, international group looking at the Papanicolaou Society and Japanese Society of Clinical Cytopathology systems to establish an international system

IAC Breast Group: Aims

• Produce a comprehensive standardized approach to breast FNAB
• Establish best practice guidelines covering:
  1. Indications and role of FNAB
  2. Technique of FNA biopsy, smear making and material handling
  3. Precise terminology for five well defined categories
  4. Key diagnostic cytopathological criteria for lesions in each category
  5. Standardized reports that are uniform and reproducible
  6. Ancillary diagnostic and prognostic testing that is appropriate
  7. Risk of malignancy for each category and link to clinical management algorithms, while recognizing that the availability of local medical infrastructure will influence the clinical approach
IAC Breast Group: Members
• Wendy Raymond (Australia), Pam Michie (South Africa), Torill Sauer (Norway), Elena Brachtel (USA), Benjaporn Chaiwun (Thailand), Bob Osamura (Japan), Lan Chen (China), Fernando Schmitt (Portugal), Philippe Vielh (Luxembourg), Andrew Field (Australia), Mary Rickard (Australia), Gary Tse (Hong Kong), Puay Hoon (Singapore), Angela Chong (Singapore), Britt-Marie Ljung (USA), Andrew Lee (UK), Luigi Di Bonito (Italy), Lauren Arnold (Australia), Dan Kurtics (USA), Davendra Segara (Australia), William Greddie (Toronto), and others.

IAC Yokohama System recommends a report format:
• Commences with one of five standard categories each described by a specific terminology.
• Followed by an assessment of the cellularity.
• Description of the key diagnostic cytopathological features that support a specific diagnosis or, if this not possible, a differential diagnosis with a preferred diagnosis.
• Diagnostic summary or conclusion.
• The aim is to achieve a reproducible and complete report that can be understood internationally by pathologists and clinicians and that will be directly linked to recommended management options.

IAC Yokohama System recommends a report format:
• There is defined terminology for each category and no reliance on using a number, which should be used only for quality assurance and research.
• Over-simplifying each case report to a number reduces the amount of information the cytopathologist gives the clinician.
• Essential that under the category heading, the cytopathologist details the specific findings and a diagnosis or DD.
• E.g., Benign category includes: cysts, fibrocystic change, fat necrosis, fibroadenomas, and intraductal papillomas which can all be categorized as 'benign', and the specific diagnosis is required to maximize correlation with imaging in Triple Test FNAB of Breast Categorisation.

Insufficient/Inadequate Definition
• The term inadequate/insufficient in breast FNAB cytology is used for slides that are too sparsely cellular or too poorly smeared or fixed to allow a cytomorphological diagnosis.
• This is a cytological assessment or diagnosis.
• Triple assessment is required where the smears do not explain or correlate with the clinical or imaging findings, but report cytology, add caveat ‘may not represent the lesion’, do not use term non-diagnostic.
• Specific reason for insufficiency should be stated.
• If there are any atypical features the lesion is atypical.

FNAB of Breast Categorisation
• Insufficient/inadequate material
• Benign
• Atypical, probably benign
• Suspicious, probably in situ or invasive carcinoma
• Malignant
• Five categories, with the ‘atypical’ maintaining high NPV of benign diagnosis, while ‘suspicious’ maintains the high PPV of malignant diagnosis, and the five categories provide risk stratification.
• ‘Non-diagnostic’ not recommended, because it can mean insufficient cells or ‘material that does not clarify the imaging findings’.

Insufficient/Inadequate
There are clinical situations where a smear may be adequate and diagnostic in the absence of epithelial cells if it correlates with the clinical and imaging findings:
• Cyst contents: proteinaceous background +/− histiocytes; state if no aseptic or other epithelium. Palpable cyst no longer palpable or the cyst seen on ultrasound is drained by the FNAB with no residual lesion.
• Fat necrosis, lipomas, spindle cell lesions, scar, hyalinized or sclerosed fibroadenomas
• BUT IF a palpable or impalpable mass lesion is seen on imaging it is suggested that a minimum of 7 epithelial tissue fragments of at least 20 cells each is required.
Factors affecting the potential inadequate rate:

1. The expertise of the FNAB operator:
   - experience of operator is directly proportional to the adequacy rate
   - pathologists compared to other staff have lower inadequate rates
   - ROSE of imaged-guided aspirates decreases insufficient rates
   - cytopathologist is immediately aware of the poor quality FNAB
   - increasing the number of needle punctures decreases insufficient rate

Factors affecting the potential inadequate rate:

2. The expertise of the direct smear-maker:
   - delay in smearing material deposited on the slide
   - failure to deliver the smears for alcohol fixation and Papanicolaou staining immediately into alcohol, and failure to rapidly air-dry slides for Giemsa staining
   - too forceful smearing leading to crush artefact
   - thick smears or smears with an excessive amount of blood
   - ultrasound gel which has not been properly cleaned from the skin and the ultrasound probe) obscuring cellular details.
   - poor ROSE or laboratory Giemsa staining

Factors affecting the potential inadequate rate:

3. The inherent qualities of some lesions produce a higher insufficient rate:
   - smaller, fibrotic and hard to stabilize lesions
   - lesions with low degree of epithelial proliferation
   - impalpable lesions accessed by ultrasound
   - invasive lobular carcinoma VS invasive ductal carcinoma NST
   - DCIS more than invasive carcinoma: expanded ducts are still a smaller target
   - necrotic or infarcted or suppurative: obscure the epithelial component.

Insufficient/inadequate: Management

- Inadequate/non-diagnostic FNAB requires review of the clinical and radiological findings to decide whether repeat FNAB or a CNB should be performed.
- If smear is technically suboptimal repeat smear recommended (ideally with ROSE).
- If imaging indeterminate/atypical further biopsy is regarded as mandatory.
- If low clinical and imaging suspicion then may follow up just with clinical and/or radiological assessment with or without FNAB.

Benign: Definition

- A benign breast FNAB diagnosis is made in cases which have unequivocally benign cytological features, which may or may not be diagnostic of a specific benign lesion.
- ROM difficult to establish because most cases do not go to surgery, but a negative clinical and/or imaging follow-up at 6 to 12 months is regarded as sufficient to record the original ‘triple negative’ diagnosis incorporating the benign FNAB as correct

Entities that fall into the benign category include:

- Acute mastitis/breast abscess
- Fat necrosis
- Cyst
- Fibrocystic change
- Normal breast tissue
- Epithelial hyperplasia
- Fibroadenoma
- Intraductal papilloma.
- Lactational change
- Adenosis and sclerosing adenosis
Benign: Management

- Benign FNAB diagnosis requires only routine clinical or imaging followup rather than CNB or excision biopsy
- Long history of utilizing breast FNAB without necessarily performing imaging; for example
- A specific benign FNAB diagnosis that correlates with the clinical findings eg. abscess yielding pus or a cyst which drains without a residual palpable nodule or a rounded firm mobile nodule with characteristic cytological features of a fibroadenoma
- Recommend correlation with imaging to achieve ‘triple test’
- FNAB should be repeated if a lesion changes its characteristics.

Atypical Definition

- The term atypical in breast FNAB cytology is defined as the presence predominantly of cytological features seen 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.
- These features include single intact cell dispersal, nuclear enlargement and pleomorphism, high cellularity, necrosis and complex architectural features suggesting micropapillary or cribriform proliferations.

Atypical

- When reporting a breast FNAB as 'atypical' the cytopathologist should always describe the material present on the slides and the degree of cellularity, and then state which specific cytological features make the lesion atypical and if possible state what the differential diagnosis is for the case.
- The causes of an 'atypical' cytological diagnosis include technical problems, scant material and interpretative problems related to the inherent characteristics of the lesion or a combination of these factors plus the expertise of the pathologist.

Atypical: related to lesion's features:

- Fibroadenoma: epithelial hypercellularity or sclerotic low cellularity
- Fibroadenoma with stromal hypercellularity Vs Low Grade Phyllodes
- Intraductal papillomas with epithelial hyperplasia
- Fibrocystic change with epithelial hyperplasia including radial scars
- Spectrum of proliferative lesions: columnar cell change, flat epithelial atypia, usual epithelial hyperplasia, sclerosing adenosis
- Lobular neoplasia: often associated with low cellularity
- Extensive necrosis or presence of mucin
- Adenomyoepithelioma
- Spindle Cell Lesions

Atypical: management

- Management requires correlation with clinical and imaging findings, in 'triple test' (which has a very high PPV and NPV); improved even further by improvements in breast U/S, tomography and MRI.
- If imaging or clinical findings are indeterminate or suspicious, CNB is recommended; if no CNB available then repeat the FNAB or simple excision biopsy
- If imaging and clinical findings are not atypical, review the patient at 3 -6 months with or without FNAB
- If no CNB or imaging available repeat FNAB recommended

Suspicious of Malignancy: Definition

- The term 'suspicious' 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 always be stated.
- Risk of Malignancy in 81 to 88%
- Suspicious category maintains the high PPV of a malignant breast FNAB diagnosis
Suspicious of Malignancy

- Technical limitations and or interpretative problems produce suspicious cytology reports.
- Limitations in specimen quality (low cellularity, thick or blood obscured, crush artefact, airdrying artefact)
- Expertise of the cytopathologist plays a smaller but still significant role
- The inherent nature of some breast lesions leads to an overlapping of cytological criteria for benign and malignant tumors, for example, fibroadenomas, epithelial hyperplasia and low grade ductal carcinoma in situ and low grade invasive carcinoma

Ductal Carcinoma in Situ

- LGDCIS and HGDCIS have different surgical pathology, molecular changes and key cytological features including different degrees of nuclear atypia and these features raise different differential diagnoses.
- CANNOT lump cytological features of LGDCIS and HGDCIS together.
- 80-85% of DCIS cases are detected in opportunistic ad hoc or organized mammography screening programs as microcalcifications, in the absence of clinical findings.
- Predominant radiological features of LGDCIS and HGDCIS are calcifications

Low Grade Ductal Carcinoma in Situ

- Cytological DD between proliferative disease and LGDCIS is challenging with overlapping diagnostic criteria.
- LGDCIS usually presents as calcifications, rarely presents as clinical mass and is an uncommon FNAB diagnosis
- When features suggest LGDCIS, should recognize them to avoid over-diagnosis of malignancy and under-calling of DCIS as proliferative breast disease
- Recommended that in cases suspicious of LGDCIS on cytological criteria, give a diagnosis of "suspicious of malignancy, raise the possibility of LGDCIS" and avoid false positive malignant diagnosis
- CNB or excision biopsy should be recommended

High Grade Ductal Carcinoma in Situ

- Extensive necrosis with calcifications and low cellularity consisting of single highly atypical epithelial cells and tissue fragments of crowded similar cells are seen in HGDCIS
- Necrosis can be seen in some high grade invasive carcinomas of no special type and in metaplastic or 'basal-type' carcinomas
- If HGDCIS is suspected consider the use of "suspicious of malignancy", raise the possibility of "carcinoma is present with features suggesting a HGDCIS component"
- Many of these cases will be called "malignant", so correlate with the imaging
- Can we diagnose absolutely the presence of invasion?
- CNB should be recommended.

High Grade Ductal Carcinoma in Situ

- Avoid an overcall of "malignancy" in cases which may be purely HGDCIS; FNAB and CNB are both sampling procedures and cannot exclude invasive carcinoma, the "triple test" is required before commencing any treatment
- Where imaging is not available, the FNAB will be of a palpable mass, which is unlikely to be pure HGDCIS
- Can FNAB diagnose invasion? Controversial, but small stromal tissue fragments infiltrated by atypical epithelial cells (same as those seen as fragmented core biopsies) matching those in the background are considered by some authors as diagnostic of invasive carcinoma but this is not always seen.

Malignant Definition

- In breast FNAB cytology, a malignant cytological diagnosis is an unequivocal statement that the material is malignant, and the type of malignancy identified should always be stated.
- A malignant diagnosis should only be made when a constellation of diagnostic criteria are identified with no discrepant findings
- None of the criteria of high cellularity, marked dispersal or nuclear atypia is individually diagnostic of invasive carcinoma and these features can be seen in proliferative and intraduct lesions.
**Malignant**

- PPV of a malignant breast FNAB diagnosis should approach 100% based on adherence to specific cytological criteria for carcinoma and other lesions applied by the cytopathologist.
- False positives: very rare and usually due to errors in interpretation of proliferative breast lesions including intraductal papillomas, fibroadenomas and adenomyoepithelioma
- False negative: frequently have minimal material or only benign elements suggesting inadequate sampling the major cause
- Discordant triple tests (eg malignant FNAB in a case with benign imaging or clinical), require further investigation prior to definitive treatment, and this is most commonly a CNB.

**Entities that fall into the malignant category #1**

- Invasive carcinoma, no special type, Grade 1 to 3
- Invasive Lobular Carcinoma
- Pleomorphic Lobular Carcinoma
- Tubular carcinoma
- Invasive micropapillary carcinoma
- Mucinous carcinoma
- Metaplastic carcinomas
- Carcinoma with medullary features

**Entities that fall into the malignant category #2**

- Carcinomas with apocrine features
- Carcinomas with neuroendocrine features
- Secretory carcinoma
- Adenoid cystic carcinoma
- Glycogen rich clear cell carcinoma
- Histiocytoid carcinoma
- Non Hodgkin Lymphoma
- Metastatic Carcinoma

**Malignant: Management**

- A malignant FNAB diagnosis requires further workup including CNB or excision biopsy.
- If the FNAB diagnosis does not correlate with the imaging findings, then CNB or if CNB is not available, further FNAB or excision biopsy is mandatory.

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**IAC Yokohama System for Reporting Breast FNAB**

- Five defined categories directly linked to management recommendations, which will increase the usefulness of breast FNAB to clinicians
- Management options depend on local medical infrastructure so that the System can be used internationally.
- Forthcoming textbook/atlas includes key diagnostic cytopathological criteria of lesions of the breast to improve interpretation of breast smears
- System will generate retrospective and prospective studies to test and establish the veracity of its five category system and refine the ROM.
- Recommends ROSE: reduces inadequate rates, increases benign and malignant diagnoses, facilitates cost effective triage, including the decision when to perform a CNB.
- ROSE by cytopathologists provides a provisional diagnosis that facilitates patient care and reduces patient anxiety.