



Diagnosis of breast lesions: fine-needle aspiration cytology or core needle biopsy? A review

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ABSTRACT

Diagnosis of breast lesions is routinely performed by the triple assessment of a specialised surgeon, radiologist and pathologist. In this setting, fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) are the current methods of choice for pathological diagnosis, both with their specific advantages and limitations. Evidence-based literature discussing which of both modalities is preferable in breast lesion diagnosis is sparse and there is no consensus among different specialised breast cancer centres. This study reviews FNAC and CNB for diagnosing breast lesions, comparing methodological issues, diagnostic performance indices, possibilities for additional prognostic and predictive tests and cost effectiveness. Overall, CNB achieved better sensitivity and specificity especially in those lesions that were not definitively benign or malignant, non-palpable and/or calcified lesions. Although FNAC is easier to perform, interpretation requires vast experience and even then, it is more often inconclusive requiring additional CNB. The authors conclude that overall CNB is to be preferred as a diagnostic method.

Diagnosis of breast lesions is routinely performed by the combined assessment of (at least) a specialised surgeon, radiologist and pathologist, usually through a multidisciplinary meeting. Fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) are currently widely used methods for pathological diagnosis, both with their specific advantages and limitations. Evidence-based literature discussing which of the modalities is to be preferred for the diagnosis of breast lesions is sparse and there seems no real consensus on their place, even among specialised breast cancer centres, although some centres tend to favour CNB in specific cases.^{1–2} In this article, we will review FNAC and CNB for breast lesion diagnosis, comparing methodological issues, diagnostic performance indices, possibilities for additional prognostic and predictive tests and cost effectiveness.

DIAGNOSTIC PERFORMANCE INDICES

As for any diagnostic procedure a high negative predictive value is important to minimise under-treatment; a high positive predictive value reduces the risk of overtreatment. Therefore, high sensitivity and specificity are crucial as they are the key determinants of both negative and positive predictive values. The overall sensitivity and specificity of FNAC and CNB in the classification of breast lesions depend on variables intrinsic to the technique as well as related to radiological/clinical and histological features. Comparison of results of the

different studies on the performance of FNAC and CNB that have not standardised these parameters may not be fully possible. Studies comparing the accuracy of FNAC and CNB within the same patient population are relatively scarce. Nevertheless, overall but not invariably, CNB has both higher sensitivity and specificity than FNAC in diagnosing benign and malignant lesions (figure 1).^{3–31} One of the largest studies so far reported sensitivity, specificity, positive and negative predictive values of 97.1%, 99.1%, 99.3% and 96.2% for FNAC.²¹ However, it should be noted that the study included only definitive benign and malignant lesions, ignoring the atypical and suspicious categories, which account for up to 20% of breast lesions in daily pathology.²¹ Indeed, Westenend *et al*⁸ reported that the positive predictive value of FNAC for malignancy was comparable with CNB (ie, 99–100%), but that this rate decreased to 78% for suspicious lesions (100% for CNB) and was only 18% in case of atypia (80% for CNB). So, in general CNB achieved higher performance indices when compared with FNAC across different studies.

PROCEDURAL (DIS)ADVANTAGES

FNAC and CNB are methodologically different and have their own advantages and disadvantages. In general, FNAC is more suitable for patients on anti-coagulants and for lesions close to the skin, chest wall, vessels and implant or for very small lesions and those that are deep seated and difficult to reach. For accessible, palpable lesions FNAC can be performed relatively straightforwardly and takes approximately 5 min in experienced hands. Therefore and for these cases, FNAC is easier to plan than CNB in an outpatient clinic. This advantage is often used as a strong argument in favour of FNAC over CNB, although it can be (partly) circumvented by optimising the logistical workflow. As a general feature of cytology, good quality FNAC depends on the competence of the aspirator, and its interpretation is primarily determined by the skills and experience of the (cyto)pathologist.^{26–32–34} The main complication of both FNAC and CNB is pain, the intensity of which seems to correlate with the diameter of the needle, but might be influenced significantly by other factors such as stress.^{35–38} For both FNAC and CNB, infection and haematoma formation requiring medical intervention are rare (0–2%), whereas the risk of pneumothorax is very rare (<0.05%).^{13–39–43}

DEPENDENCE OF DIAGNOSTIC PERFORMANCE ON CLINICAL/RADIOLOGICAL FEATURES

The success rate of FNAC for obtaining a definite (malignant) diagnosis depends both on the

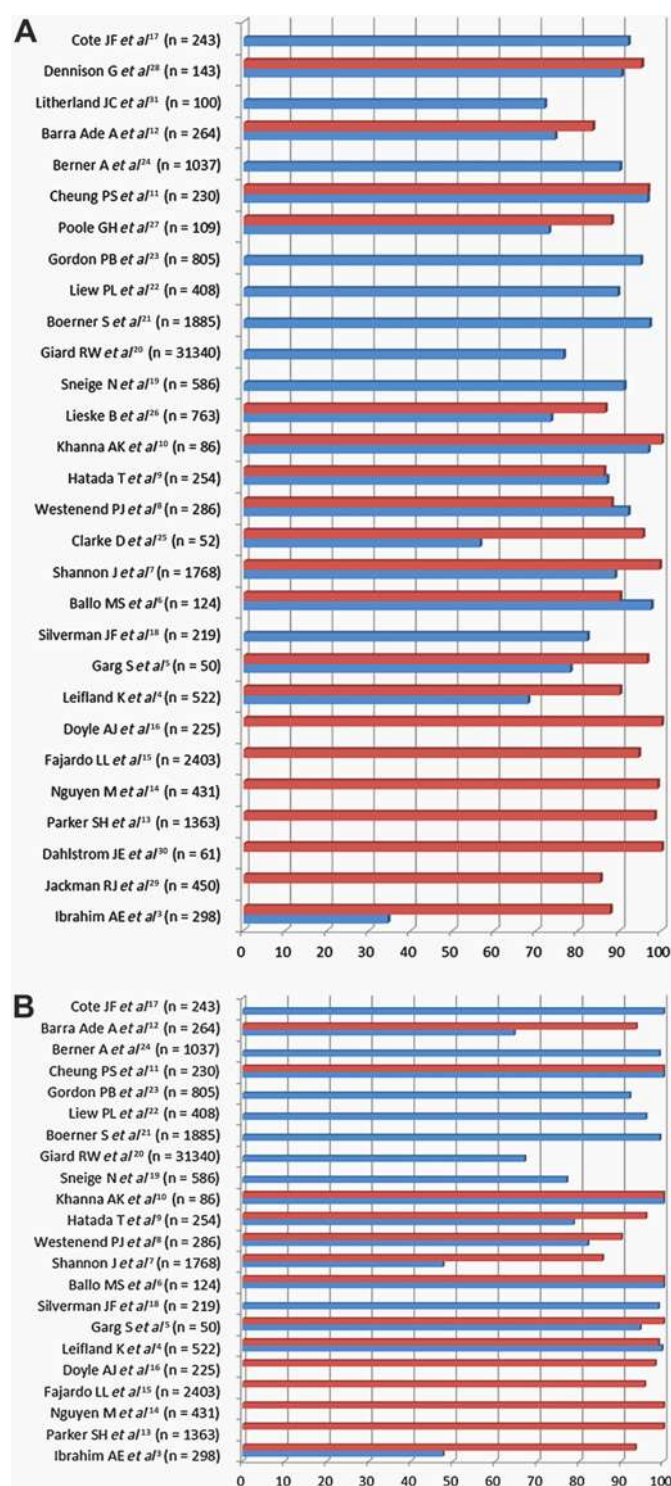


Figure 1 Sensitivity (A) and specificity (B) of fine-needle aspiration cytology (FNAC) and core needle biopsy (CNB) in diagnosing malignant breast tumours. top bar: CNB; lower bar: FNAC. The sensitivity of FNAC in different studies (from 35% to 95%) showed more variability and was generally lower compared with CNB (ranging from 85% to 100%). The specificity of FNAC (ranging from 48% to 100%) was also generally lower than CNB (ranging from 86% to 100%).

palpability and size of the lesion. FNAC has average success rates of 75–90% for palpable and 34–58% for non-palpable breast lesions, whereas success rates for CNB were 97% and 94%, respectively.^{3 44 45} FNAC has a success rate of only 50% for

lesions less than 10 mm, while CNB is successful in over 90% of such lesions. Therefore, the success rate of FNAC seems to be especially low for non-palpable lesions and for those smaller than 10 mm.⁴⁶ Accuracy rates for FNAC are also decreased for large tumours (>4 cm) and calcified lesions are also significantly associated with a higher rate of insufficient sampling than masses.^{45 47–49}

DEPENDENCE OF DIAGNOSTIC PERFORMANCE ON HISTOLOGICAL FEATURES

Apart from radiological and clinical features, diagnostic accuracy predominantly depends on the morphological diagnosis in various studies.

(Pre)malignant lesions

An important issue in daily practice is discrimination between in-situ (eg, ductal carcinoma in situ; DCIS) and invasive lesions. Although, per definition, cytology is unable to make the claim of invasion in the strictest sense of the word (ie, invasion through the basal membrane), several studies reported criteria to predict invasion on the basis of cytological features. These include infiltration in fragments of fat, infiltration in fibrous tissue fragments, proliferation of fibroblasts and elastoid stromal fragments. The first two features are considered to be most important, although pre-existent ducts can also be surrounded by fat in physiological conditions, and over-interpretation of these criteria has led to false positive cases.⁵⁰ The overall sensitivity and specificity of the aforementioned criteria are, however, low, with 38% of invasive carcinomas showing none of these criteria, while 29% of DCIS showed at least one.⁵⁰ In particular, diagnosis of tubular carcinoma and invasive lobular carcinoma is more difficult on FNAC than on CNB. So, even with these criteria in hand, it is very difficult to affirm invasive carcinoma by FNAC whereas it is much easier to do using CNB. It is worth mentioning that approximately 20% of patients with a CNB diagnosis of DCIS have invasive carcinoma in the excision specimen. This proportion varies according to the gauge of needle.⁵¹ CNB is also a more robust method to distinguish between invasive lobular and invasive ductal carcinoma, based on histological and immunohistochemical features. This preoperative distinction may be clinically relevant for: (1) planning the extent of the surgical operation especially if they are considering breast-conserving surgery; (2) considerations regarding neoadjuvant chemotherapy; and (3) the increased risk of contralateral disease in the case of invasive lobular carcinoma warranting contralateral radiological examination (MRI).^{52–55}

High-risk lesions

CNB is an accurate method to diagnose so-called high-risk lesions such as atypical ductal hyperplasia, lobular carcinoma in situ, atypical papillomatosis and columnar cell lesions. Recognition of these lesions is important as they can mimic, and are often associated with, further advanced lesions, and indicate an increased risk of invasive cancer during follow-up.^{56 57} The increased use of vacuum-assisted biopsies and the intact biopsy procedure, by which a semi-invasive mini-resection can be performed, has raised the question of whether an open surgical excision is always warranted for these lesions.⁵⁸ The intact biopsy procedure, which differs from core devices in that it removes one spheroid specimen rather than smaller cylindrical cores, can be performed safely and accurately and tends to have fewer underestimations of DCIS compared with CNB.^{58 59}

Papillary lesions

Papillary lesions comprise a spectrum from benign duct papilloma to papillary carcinoma. In general, the diagnostic accuracy of FNAC for papillary lesions is variable but low.^{60–63} Cytological features to distinguish between benign and malignant papillary lesions include papillary fronts, overall cellularity, epithelial cell balls, single cells (with or without atypia) and plasmacytoid cells. These criteria are helpful but not unanimous, and the overall accuracy of FNAC to predict benign from malignant papillary lesions is poor, especially for diagnosing malignant lesions.⁶¹ The accuracy of CNB in the histological diagnosis and classification of papillary lesions in the breast is also moderate. The most difficult differential diagnosis is between papillary carcinoma *in situ* and papilloma, especially if the latter is complicated by florid epithelial hyperplasia, atypical hyperplasia or carcinoma *in situ*. Immunohistochemistry has recently been shown to be helpful as benign papillary lesions can express high molecular weight cytokeratins (CK5/6, CK14, 34βE12), are surrounded by myoepithelial cells and show heterogeneous staining for oestrogen receptor (ER).^{60 64 65} However, false positive and false negative interpretation cannot be excluded and surgical (diagnostic) excision for papillary lesions is recommended, although removal with a vacuum-assisted biopsy device is a reasonable option if there is no atypia on the core biopsy.

Fibroepithelial lesions

Fibroepithelial lesions of the breast encompass commonly occurring fibroadenomas and rare phyllodes tumours.⁶⁶ The latter can be potentially malignant and require complete excision with an adequate margin to prevent recurrences.⁶⁷ The differential diagnosis between both entities by FNAC is challenging and is hampered by the shortage of universally accepted cytological criteria.⁶⁸ Immunohistochemistry on CNB has recently been shown to be helpful, although its use in routine practice is still limited and setting reliable cut-off values is hampered, for example, for Ki-67, which shows a large overlap between phyllodes tumour and fibroadenoma.⁶⁹ Accuracy rates by FNAC and CNB are moderate to high, respectively.^{70 71} Regarding the grade of phyllodes tumours, both FNAC and CNB perform suboptimally. This is mainly due to the heterogeneity of phyllodes tumours with regard to both stromal cellularity and (lack of) epithelial atypia. On one hand, sampling areas with only low cellularity of a relatively large amount of sheets of epithelial cells with only mild atypia increases the risk of underestimation of the severity of the lesion. On the other hand, an epithelial proliferation with mild atypia and limited discohesion in a FNAC of a histologically unsuspecting fibroadenoma may result in overestimation of the severity of the lesion.

Normal breast tissue versus benign lesions

As a general rule, a definite benign diagnosis and distinction between benign and normal breast tissue can be made on CNB. By comparison, benign and normal lesions are often difficult to distinguish with FNAC.

Calcifications

The assessment of calcification in a core biopsy is much more sophisticated than in FNAC, as the calcification can be seen in the tissue section within the lesion. Moreover, CNB enables a comparison of the pattern of calcification in the core biopsy with that seen on the x-ray. This is why in the UK breast screening programme it is recommended that core biopsy, rather than FNAC, is used for the assessment of calcification.

ASSESSMENT OF PROGNOSTIC AND PREDICTIVE BIOMARKERS

The increased use of neoadjuvant therapy has prompted the need for reliable preoperative assessment of histological and immunohistochemical prognostic and predictive features. For example, grading of malignant breast tumours is an independent prognostic factor. Cytological grading on FNAC correlates quite well with histological grading on CNB and morphometry on FNAC has been shown to be of some help.^{72–74} However, as FNAC cannot reliably discriminate between DCIS and invasive carcinoma, the value of the cytological grade of a malignant FNAC remains unclear. Moreover, correlation in grade between CNB and excision specimens on H&E slides is limited, sometimes with an underestimation on biopsy, but better concordance can be obtained with additional immunohistochemical markers although there is no overall agreement on cut-off values.^{75–83} Therefore, despite some centres assessing histological grade on immunohistochemical/H&E staining, this is not recommended, neither on FNAC nor on CNB.

In the (neo)adjuvant setting, assessment of ER, progesterone receptor (PR) and HER2 status is crucial and receptor status is routinely determined on (preoperative) biopsies in many pathology laboratories. It is generally accepted that ER, PR and HER2 can be reliably assessed on CNB but not on FNAC.^{84 85} The same holds true for proliferation assessment, which is part of grading and is prognostically very important.⁸⁶ During the past decade with the introduction of small molecule inhibitors, molecular profiling of (breast) tumour samples is increasingly important. In this respect, it is noteworthy that CNB contains RNA/DNA in a sufficient amount and of sufficient quality for molecular testing (eg, arrays), whereas this can be problematical in the case of FNAC in which the yield is often limited.

COSTS AND SPEED

There is no doubt that the technical costs for a single FNAC is lower than for CNB. However, the overall costs do not only depend on the procedural costs of one sampling procedure, but on the total costs to obtain a reliable definitive diagnosis. In this respect, CNB might paradoxically even be superior to FNAC, at least in selected cases. FNAC may be more cost effective for palpable lesions (with inadequacy rates of <10%), the additional cost for imaging guidance required for non-palpable lesions makes this procedure less cost effective in general.^{18 45 87} Even with imaging guidance, the rate of insufficient samples yielded by FNAC varied between 29% and 39%. An interesting study showed that indefinite diagnosis using FNAC required additional CNB in 32% (93/289) of cases and additional surgical excision biopsies in 21% (62/289) of cases versus 1% (2/214) and 15% (33/214) after CNB, respectively.⁴⁴ Therefore, although cheaper as a single sampling procedure, FNAC requires additional histological tissue sampling (CNB and surgical excision biopsy) in a significant number of cases due to its lower accuracy. This stresses the important point that for final accurate diagnosis, routinely performing FNAC as an initial diagnostic procedure may be even more expensive than CNB, although these results need to be confirmed in larger cohorts.

A high quality of patient care stands with a correct diagnosis as well as the efficacy to come to an optimal plan of treatment. So, the actual speed to come to a definite diagnosis matters. For FNAC, a routine May–Grunwald–Giemsa staining takes up to 1 h, whereas a so-called Quick-diff enables a diagnosis in only 5 min, which provides a same-day diagnosis. The standard processing time to get to a histological diagnosis is usually approximately 24 h. However, ultrafast tissue processing

procedures now allow an accurate histological diagnosis within 4 h after sampling. FNAC might thus eventually result in a (only slightly to moderately) faster diagnosis, which is mainly relevant for patient comfort in the case of a benign diagnosis and no need for direct further treatment. However, this speed advantage in diagnosis becomes more relevant in the case of a malignant diagnosis, which requires discussion in a multidisciplinary team involving at least a surgeon, radiologist, medical oncologist, radiation oncologist and pathologist. Although some large centres can provide a frequent multidisciplinary meeting, which allows same-day discussion and therapy planning in a one-stop outpatient clinic in the case of FNAC, this is not an attainable option for most centres. It is our experience that a window of 36 h after CNB is in most cases sufficient to come to a definite and reliable diagnosis prior to such multidisciplinary meeting. In this workup scheme, patients get not only the final diagnosis but also the treatment plan right after the multidisciplinary meeting when they return to the outpatient clinic. Therefore, in the case of a (potentially) malignant breast lesion, the overall speed advantage of FNAC over CNB is relative. Noteworthy is that modified core wash cytology has been shown to correlate well with histology, with a sensitivity and specificity of 97% and 100%, respectively. Combining this technique or imprint cytology with CNB histology may improve the quick and reliable diagnosis of malignant breast lesions.⁸⁸

CONCLUSIONS

The diagnosis of breast cancer is usually accomplished by triple assessment (surgeon, radiologist and pathologist) in a multidisciplinary setting. FNAC and CNB are the most commonly used diagnostic modalities in the morphological diagnosis of breast tumours. In experienced hands, the sensitivity of FNAC is high, and not much lower than CNB. The specificity of CNB is,

Key messages

- ▶ FNAC and CNB are commonly used diagnostic modalities for breast lesions.
- ▶ Both have their own advantages and limitations.
- ▶ In general and based on overall performance indices, CNB is to be preferred over FNAC for the diagnosis of breast lesions.

however, higher as well as the positive predictive value for suspicious and especially atypical lesions and fibroepithelial lesions. Also, the inadequacy rate of FNAC for non-palpable lesions, the incidence of which has increased as a result of widely used screening programmes, is higher than for CNB. So, the overall performance indices of CNB are superior to FNAC in the majority of breast lesions. Ancillary immunohistochemical and molecular tests are more reliably and more easily performed on CNB than on FNAC, which is relevant to determine additional prognostic and predictive markers. Moreover, because of the increase in (neo)adjuvant treatment options, immunohistochemical and molecular profiling of individual tumour samples is increasingly important, especially in this new era of personalised medicine. Regarding cost effectiveness, the total costs to obtain a definitive, reliable diagnosis seem to be even higher for FNAC because of its low accuracy rate, especially for non-palpable and small lesions. FNAC is fast and therefore might be preferred for some palpable, probably benign lesions. In the case of (potential) malignancy, the speed advantage of FNAC over CNB seems relatively irrelevant in view of the required multidisciplinary meeting to arrive at a therapy plan. Therefore, taking into account the benefits and limitations of both techniques (table 1), we argue that CNB is to be preferred over FNAC for the diagnosis of breast lesions.

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Table 1 Summary of benefits and limitations of FNAC and CNB

	FNAC	CNB
Procedural (dis)advantages		
Accessibility of deep sites	Yes	No
Level of experience required	High	Average
Success rate	60–75%	99%
Complication rate	Very low	Low
Diagnostic performance dependent on clinical/radiological features		
Non-palpable tumours	Low	High
Palpable lesions	High	High
Size <10 mm or >40 mm	Low	High
Diagnostic performance dependent on histological features		
Distinction between in-situ and invasive cancer	No	Yes
Diagnosis of pre-invasive lesions (CCL, ADH)	Low	High
Diagnosis of papillary lesions	Low	Moderate
Distinction between fibroadenoma and phyllodes tumour	Moderate	High
Assessment of prognostic and predictive biomarkers		
Grading	Low	Moderate
ER/PR assessment	Low	High
HER2 assessment	Low	High
Proliferation assessment	Moderate	High
DNA/RNA isolation for molecular test	Low	High
Cost/speed effectiveness		
Speed	High	Moderate
Costs*	Very low	Low

*Costs: fine-needle aspiration cytology (FNAC) is cheaper as a single procedure but is overall likely to be more expensive to obtain a definitive diagnosis because of lower accuracy rates often necessitating additional core needle biopsy (CNB) or surgical excision. ADH, atypical ductal hyperplasia; CCL, columnar cell lesion; ER, oestrogen receptor; PR, progesterone receptor.

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