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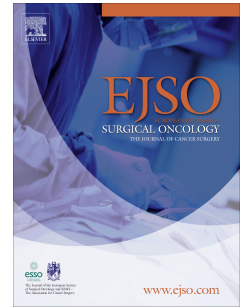
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## Preoperative cytological and histological diagnosis of breast lesions: a critical review

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### Statement of expertise

The first author, BK, has recently published several papers on fine needle aspiration, core needle biopsy and nipple discharge cytology.

CW is an experienced pathologist and cytopathologist with special scientific interest in the position the diagnostic pathology in preoperative work-up of breast lesions.

LS is a breast surgeon with special interest in preoperative work-up and has supervised several research projects on this subject in the past years.

The senior author, TW, is an experienced professor in surgical oncology with special interest in diagnosis and surgical treatment of breast pathology.

### Key words

Breast pathology; fine needle aspiration; core needle biopsy; core wash cytology; touch imprint cytology; breast surgery.

## ABSTRACT

### Background

Non-operative pathology diagnoses constitute an essential part of the work-up of breast lesions. With fine needle aspiration (FNA) and core needle biopsy (CNB) both having unique advantages, there is an increasing acceptance of CNB. This paper aims to outline the scientific basis of this trend.

Additionally, we provide an update on novel techniques that derive cytological specimens from CNB (i.e., touch imprint (TI) and core wash (CW) cytology) in an attempt to get the best of both worlds.

### Methods

In addition to using the authors' experience, we performed a search of the Medline database combining the search terms “breast cancer diagnosis”, “core needle biopsy”, “fine needle aspiration”, “touch imprint cytology”, “core wash cytology” and “complications”.

We defined a conclusive non-operative diagnosis as “malignant” in lesions that were malignant on follow-up and “benign” in lesions that were benign on follow-up.

### Results

CNB was more often conclusive than FNA in benign and malignant lesions in 4 prospective studies. Although the more rapid diagnoses by FNA result in less patient anxiety during diagnostic work-up, CNB allows for fairly reliable estimation of invasion, histological type, grade, and receptor expression. CW and TI cytology seem promising techniques with conclusiveness rates that are roughly comparable to that of FNA.

### Conclusions

All new suspicious breast lesions require careful non-operative investigation by CNB. However, additional cytological assessment by FNA can still be useful as a same-day diagnosis decreases patient anxiety and facilitates surgical treatment planning. TI and CW cytology techniques are promising same-day diagnosis modalities.

## INTRODUCTION

Present-day non-operative diagnosis of palpable breast lesions comprises ‘triple assessment’ by physical examination, imaging (mammography and/or ultrasound (US)), and pathology (fine needle aspiration (FNA) or core needle biopsy (CNB)).[1,2] This diagnostic work-up precludes standard excisional biopsy when all three components of the triple assessment are conclusively positive (~100% probability of malignancy) or conclusively negative (~100% probability of a benign lesion).[3-5]

Cytological and histological specimens are conventionally diagnosed as “inadequate”, “benign”, “atypical”, “suspicious”, or “malignant” (**Table 1**). The diagnostic value of a needle biopsy depends on whether it yields a decisive and accurate diagnosis. This is what we define as a *conclusive* diagnosis in this paper. Specifically, a conclusive diagnosis by FNA or CNB is defined as a ‘benign’ diagnosis (C2/B2) in a truly benign lesion and a ‘malignant’ diagnosis (C5/B5) in truly malignant lesions. Consequently, we will refer to diagnostic ‘conclusiveness’ as the proportion of “benign” (C2/B2) diagnoses in benign lesions and as the proportion of “malignant” (C5/B5) diagnoses in malignant lesions.[6]

Due to the introduction of nationwide mammographic screening programmes, however, the proportion of small, nonpalpable breast lesions presenting as microcalcifications on mammography has risen.[7,8] Additionally, the increasing use of magnetic resonance imaging (MRI) screening in high-risk women has further increased the number of small tumours in which malignancy can only be excluded or confirmed conclusively by MRI-guided percutaneous needle biopsy.[9] As such, the role of a pathology diagnosis in stratifying patients to surgery or clinical follow-up has increased and surgeons’ confidence in such decisions depends upon the conclusiveness of non-operative pathology diagnoses.[10]

While FNA is a traditional modality that has been used as a rapid and safe tool for distinguishing benign from malignant breast lesions,[11] CNB has been increasingly employed since the 1980’s. Its main advantage is that it provides preoperative knowledge of a histological diagnosis and prognostic factors.[12] Vacuum assisted biopsy (VAB) systems are recent large-core variants of CNB.

With cytology and CNB both having unique advantages, there is an increasing acceptance of CNB for evaluating breast lesions.[10,13] This paper aims to outline the scientific basis of this trend, focussing on diagnostic accuracy, impact on surgical management, prognosis assessment and complications of these modalities. Finally, we will discuss needle biopsy techniques that combine cytology and histology.

## DIAGNOSTIC ACCURACY

### *Comparative accuracies*

The histological sample collected by the large-calibre, 7-18 Gauge needles used for CNB allow for a tissue diagnosis and could rationally be expected to yield more representative and more readily interpretable material than the smaller 20-25 Gauge FNA needles that only allow for cytological examination. Many authors have claimed CNB to have superior diagnostic accuracy based on solely historical comparisons of CNB and FNA series.[14-16]

In fact, few studies have directly compared FNA and CNB regarding their diagnostic accuracies that is, they prospectively investigated the same patients with both modalities (**Figure 1**).[17-23] In these studies CNB has repeatedly, but not invariably, been shown to yield more conclusive diagnoses than FNA in both malignant and benign lesions. This implies that CNB is imperative to the treatment planning of all breast lesions.

However, this does not exclude FNA from the preoperative pathology work-up. In fact, combining both modalities may result in an even higher conclusiveness. Specifically, using FNA in conjunction with CNB may increase conclusiveness rates with 5%-16% in malignant lesions and with 0%-2% in benign lesions.[19,21,23] As such, the role of FNA as complementary to CNB, facilitating definitive exclusion or confirmation of malignancy in case of an indeterminate CNB, has been suggested.[17] Yet, indeterminate primary FNA invariably mandate a CNB.[24]

### *Factors affecting conclusiveness*

Generally, diagnostic modalities that yield consistently conclusive results irrespective of the operator and interpreter involved are most useful to breast pathology patients. Specimen adequacy is considered

to be less operator-dependent for CNB than for FNA,[25] but operator experience has been identified to impact CNB success and no study has compared this in relation to FNA.[26,27] As for microscopic assessment, CNB has been shown to produce highly reliable results in a study of more than 2400 biopsies, with a chance-corrected interobserver agreement ( $\kappa$ ) of 0.90.[28] In contrast, FNA conclusiveness varies significantly among pathologists, but is not affected by the amount of experience in cytopathology.[29] Currently however, it cannot be estimated which modality yields the most consistent results as no directly comparative studies exist.

Irrespective of these flexible parameters, relatively simple clinical and radiologic lesion characteristics can serve to predict whether an FNA or CNB will be informative. For FNA, small (<1 cm) and large (>4 cm) tumours, freehand aspiration and lesions appearing as microcalcifications on mammogram have been associated with inconclusive diagnoses.[30-33] In contrast, CNB, especially VAB which samples a greater tissue volume, exhibits comparable conclusiveness rates in microcalcifications and masses.[27,34]

Even after aspiration, FNA conclusiveness can be increased by having an on-site cytopathologist assessing specimen adequacy[35] and by processing the aspirate to create a monolayer preparation (versus directly smearing it) in the laboratory.[36]

## IMPACT ON SURGICAL MANAGEMENT

Obviously, conclusively benign FNA or CNB diagnoses obviate the need for excisional biopsy, provided that imaging and examination are concordantly benign,[4,37,38] and reducing redundant surgeries is in fact one of the major goals in breast care.[39] Similarly, conclusive FNA or CNB decrease the number of surgical procedures in malignant lesions.[37,40] Accordingly, both FNA and CNB are cost-effective modalities.[41,42]

Yet, important differences between FNA and CNB exist (**Table 2**). FNA allows for a rapid diagnosis within 30 minutes, providing immediate reassurance to the majority of patients with benign disease and minimizing the psychologically stressful period of waiting for a malignant diagnosis.[43,44] In a 670-patient randomized controlled trial, patients attending a one-stop breast

clinic were less anxious on the short term than those randomized to delayed discussion of diagnostic results.[45] Additionally, direct conclusive diagnoses obviate further review appointments in patients with benign lesions and facilitate the surgical scheduling in breast cancer patients.[45] However, FNA cannot accurately assess histological information key to adequate surgical treatment planning for malignancies. Here lies the main advantage of CNB.

First, CNB can differentiate between ductal carcinoma in situ (DCIS) and invasive ductal carcinoma. This conveys important information since pure DCIS lesions often require larger tissue removal and only necessitate sentinel node biopsy in selected cases.[46-48] However, due to selective sampling, invasion is underestimated in 9%-38% of cases showing DCIS on CNB.[27,40,48-50] Consequently, these patients will require a second operative procedure for axillary staging. As for FNA, having similar sampling problems for DCIS, specimens lack sufficiently specific cytomorphological aspects to predict invasion or absence thereof.[51,52] Therefore, all patients with a malignant FNA diagnosis should have sentinel node biopsy to ensure adequate axillary staging for invasive cancers. However, the patients who ultimately prove to have pure DCIS will have an unnecessary sentinel node biopsy. As such, many centres prefer CNB to individualize the choice to perform axillary staging.

Second, CNB can better distinguish invasive lobular from invasive ductal carcinoma than FNA as the infiltrating pattern is characteristic on histology and epithelial markers can confirm the diagnosis.[53,54] Preoperative knowledge of specific tumour histology is fundamental to planning the extent of surgery since lobular carcinoma carries an increased risk of positive lumpectomy margins and synchronous contralateral disease.[55,56]

Nevertheless, the more specific nature of histological diagnoses provided by CNB also poses therapeutic dilemmas when B3, 'high-risk' lesions are found on CNB. These include atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), atypical papillomatosis, flat epithelial atypia and radial scars/complex sclerosing lesions. As these lesions can mimic and, if diagnosed correctly, can be associated with malignancy,[57,58] possible underestimations of surrounding DCIS and invasive cancer should be kept in mind. As such, surgical excision is warranted in lesions with high underestimation risks, such as ADH.[58] Although the increasing use of large-bore VAB reduces the



risk of missing adjacent cancer by sampling more breast tissue, more patients with benign disease will accidentally be found to have borderline lesions and may have redundant excisions or follow-up.

### **ASSESSMENT OF PROGNOSTIC AND PREDICTIVE FACTORS BY PERCUTANEOUS NEEDLE BIOPSY**

The increasing use of neoadjuvant therapy has resulted in a more frequent need for knowledge of prognostic and predictive tumour characteristics.[59] These include histologic grade and subtype, estrogen receptor (ER), progesterone receptor (PR) and HER2-neu status, and are key to planning both neoadjuvant and adjuvant treatment when neoadjuvant therapy is considered. Additionally, the type of medical therapy is partly determined by receptor expressions in patients unfit for excision or in patients who present with metastatic disease. CNB is considered to provide reliable assessments of prognostic and predictive factors, exhibiting high concordance rates with surgical specimens for tumour grade (59%-91%), ER status (78%-100%), PR status (71%-91%) and HER2-neu status (60%-100%).(reviewed in[60])

There have been successful attempts to assess receptor expression on FNA specimens,[61,62] however, accurate assessment of histological grade is only possible on CNB. Yet, grade may still be underestimated by CNB due to regional differences in primary tumour differentiation,[63] Although cytological grading on FNA specimens has been shown to correlate with histologic grade,[64] its relation with histological grade on the surgical specimen, response to chemotherapy and prognosis is unknown. Also, as FNA cannot discriminate between DCIS and invasive carcinoma, the meaning of a given cytological grade for malignant FNA remains unknown.

### **COMPLICATIONS**

The main complication of both FNA and CNB is pain during the biopsy procedure. It seems obvious that larger needles would cause more biopsy-related pain, as measured by a validated visual analogue scale.[65] This has indeed been demonstrated in a randomized controlled trial on 104 patients comparing 23-gauge and 21-gauge FNA and in a prospective cohort study comparing 21-gauge FNA

and 14-gauge CNB.[66,67] Contrarily, in a recent prospective cohort study of 220 biopsies, patients undergoing 21-gauge FNA had significantly more pain than those having 14-gauge CNB or 11-gauge VAB.[68] However, this study did not adjust for patient-related factors that may influence pain perception, such as psychological distress.

By directing FNA and CNB needles towards the chest wall, pneumothorax may occasionally result, especially in the tail of the breast. However, larger series have reported pneumothorax rates of only 1 and 5 in 10 000 cases for FNA and CNB, respectively.[69,70]

Hematoma formation can be expected after any needle biopsy, but hematomas requiring intervention are uncommon, occurring in less than 1% of both FNAs and CNBs.[70-73] Similarly, needle tract infection is an infrequent complication, with reported rates of 0-2% and 0.01%-0.2% for FNA and CNB, respectively.[70,72-74]

Additionally, malignant cells may be displaced along the needle tract in up to 50% of breast cancers sampled by CNB, [75-77] while for FNA no recent data are available. However, it is unlikely that malignant cell seeding impacts recurrence and survival.[78,79]

## COMBINING CYTOLOGY AND HISTOLOGY IN PREOPERATIVE WORK-UP

In an attempt to combine the unique benefits of a same-day diagnosis, enhanced diagnostic accuracy and histological information in a single percutaneous needle biopsy, laboratory techniques that derive cytological specimens from CNBs have been investigated recently. Touch imprint (TI) cytology involves smearing the CNB specimen onto a microscopic slide prior to final formalin fixation. Alternatively, core wash (CW) cytology specimens are prepared by washing the tissue contained in the needle notch in a saline or cell-preserving solution. For CW, either a smear, involving air drying of the cell-containing solution, or a liquid-based preparation, using a cytocentrifuge, is then created.

Similar to FNA, the success of TI and CW cytology depends on the conclusiveness with which a preliminary diagnosis can be given to the patient. The results of studies focussing on the conclusiveness of these modalities are summarized in **Table 3**.

Studies on TI cytology have found conclusiveness rates ranging from 44-93% in benign lesions and from 42%-100% in malignant lesions.[80-89] Unfortunately, only 2 studies used the final

diagnosis by surgical or clinical follow-up as the gold standard.[85,87] Conversely, the other studies only correlated TI cytology diagnoses to the later CNB diagnoses (a surrogate gold standard assessment). As CNB can miss cancers and falsely diagnose non-malignant lesions as malignant (**Figure 1**), the true conclusiveness of TI cytology may have been under- or overestimated in these studies.

The use of CW cytology has been questioned due to conclusiveness rates in both benign and malignant lesions being lower than 40%.[90,91] In a prospective study of 236 benign and 210 malignant cases, Uematsu and Kasami found 42% of CW samples to be inadequate (C1). Therefore, they concluded that CW is not useful for same-day diagnosis of breast lesions.[91] Contrarily, in a small prospective laboratory study using a modified CW procedure on 30 breast lesions only 1 specimen was found to be inadequate.[85] This resulted in higher conclusiveness rates than those previously found.

The same study explored whether CW and TI cytology had different conclusiveness rates in the same patient population. Conclusiveness was demonstrated to be identical in malignant lesions (both 75%), but slightly higher for CW cytology in benign lesions (89% vs. 67%, respectively,  $P=.26$ ).[85] Yet, the true comparative conclusiveness rates are currently unknown as larger studies are lacking.

From the results of the above studies, it is apparent that TI and CW cytology are promising relatively new techniques that frequently enable a same-day diagnosis of benign or malignant breast lesions.

## CONCLUSIONS

All new suspicious breast lesions require careful non-operative investigation by CNB. This is mainly because of its superior diagnostic accuracy, its potential to distinguish in situ from invasive carcinoma and its ability to assess prognostic and predictive tumour characteristics. However, additional cytological assessment by FNA can still be useful as a same-day diagnosis decreases patient anxiety and facilitates surgical treatment planning. TI and CW cytology techniques seem accurate alternative same-day diagnosis modalities.

## CONFLICT OF INTEREST STATEMENT

We had no relationship with other persons or organisations, both financial and personal that could potentially bias the present work.

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**FIGURE CAPTION****Figure 1. Conclusiveness rates of FNA and CNB in prospective, directly comparative studies**

\*  $P < .05$

†  $P < .005$

‡  $P < .001$

Red dots delineate estimates of FNA conclusiveness, whereas blue dots delineate estimates of CNB conclusiveness. Horizontal lines correspond to 95% confidence intervals.

FNA indicates fine needle aspiration; CNB, core needle biopsy; 95% CI, 95% confidence interval.

## TABLES

**Table 1. Definition of conclusive and inconclusive diagnoses by FNA and CNB**

	Modality		Conclusive?	
	FNA	CNB	Benign follow-up <sup>a</sup>	Malignant follow-up <sup>a</sup>
Inadequate	C1	B1	No	No
Benign	C2	B2	Yes	No
Atypical	C3	B3	No	No
Suspicious	C4	B4	No	No
Malignant	C5	B5	No	Yes

<sup>a</sup> Either surgical or clinical/radiographic

**Table 2. Differences between FNA and CNB regarding their impact on the surgical management of breast lesions**

<b>Influence</b>	<b>FNA</b>	<b>CNB</b>
Same-day decision making and patient counselling	+	+/-
Preclude excision of benign lesions	+	+
Preclude excisional biopsy of malignant lesions	+	+
Differentiation of in situ vs. invasive carcinoma	-	+
Differentiation of lobular vs. ductal carcinoma	+/-	+
Accurate identification of high-risk lesions <sup>a</sup>	-	+
Complete lesion removal	-	+/-

<sup>a</sup> Such as atypical ductal hyperplasia, atypical papillomatosis, atypical lobular hyperplasia, lobular carcinoma in situ and flat epithelial atypia

FNA indicates fine needle aspiration; CNB, core needle biopsy

**Table 3. Overview of conclusiveness rates of preliminary diagnoses by touch imprint and core wash cytology**

Author [reference]	Modality	Design	N	Conclusiveness (%)		Concordance with CNB (%)
				Benign lesions	Malignant lesions	
Wauters 2009[91]	TI	Prospective	30	67	75	70
Kulkarni 2009[90]	TI	Retrospective	813	84	87	96
Oikonomou 2008[89]	TI	Retrospective	72	93	90	90
Foutou 2007[88]	TI	Retrospective	93	85	100	-
Fashid 2006[92]	TI	Retrospective	567	56	42	47
Klevesath 2005[87]	TI	Retrospective	128	63	85	91
Jones 2004[93]	TI	Prospective	111	76	81	80
Kass 2003[94]	TI	Retrospective	199	62	58	62
Green 2001[86]	TI	Retrospective	100	-	-	84
Sneige 2000[95]	TI	Retrospective	172	44	62	58
Wauters 2009[91]	CW	Prospective	30	89	75	73
Uematsu	CW	Prospective	458	32	38	33



2008[97]						
Lankford	CW					
1998[96]		Retrospective	211	85	39	83

CNB indicates core needle biopsy; TI, touch imprint cytology; CW, core wash cytology

Empty cells indicate that calculation of the respective parameter was impossible because of insufficient data presentation in the published paper

