RESEARCH COMMUNICATION

Accuracy of Fine Needle Aspiration Cytology from Breast Masses in Thailand

Sudarat Nguansangiam, Somneuk Jesdapatarakul, Siriwan Tangjitgamol*

Abstract

Objective: To evaluate the accuracy and diagnostic performance of fine needle aspiration FNA cytology in diagnoses of breast masses. Methods: Women who had FNA diagnoses for breast masses and underwent subsequent histopathologic evaluation during January 2003-December 2006 were accessed from the archive of the Anatomical Pathology Department of our institution. Cytologic diagnoses were classified as unsatisfactory, benign, atypical probably benign, suspicious probably malignant, and malignant, and were compared to the histopathologic diagnoses obtained from core needle biopsy, excisional biopsy, or mastectomy to give an assessment of the diagnostic performance of FNA. Results: A series of 190 breast masses were identified during the study period. The FNA cytological diagnosis was unsatisfactory due to inadequate specimens in eight cases (4.2%). The diagnoses in the remaining 182 cases were: benign lesions in 98 (53.9%); suspicious for malignancy in 31 (17.0%); and malignant in 53 (29.1%). From the subsequent histopathologic diagnoses, 6/98 cases of benign cytology turned out to be malignant lesions (false negatives); 22/31 cases of suspicious cytology were truly malignant while the other nine were benign; and only 1/53 with malignant cytology was benign (false positive), the lesion being a fibroadenoma . The overall accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 91.2% (95% confidence interval [CI], 87.6%-94.8%), 92.5% (95% CI, 88.7%-96.3%), 90.2% (95% CI, 85.9%-94.5%), 88.1% (95% CI, 83.4%-92.8%) and 93.9% (95% CI, 90.4%-97.4%), respectively. Conclusions: FNA cytology is highly accurate for diagnosis of breast masses. However, the clinician should correlate FNA cytological results with physical examination and imaging findings to prevent false negative and false positive events and to obtain optimal management for their patients.

Key Words: Breast masses - fine needle aspiration - diagnostic accuracy, cytology, histopathology

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Introduction

Breast cancer is the most common malignant neoplasm affecting women world wide (Pisini et al., 1993). In Thailand, it is the second most common in women after cervical cancer, with an estimated prevalence of 20.5 per 100,000 during 1998-2000 and an age-standardized incidence rate (ASR) of 24.3 (Chaiwerawatana, 2007). The incidence is increasing in the past decade, especially where it is most common, in Bangkok.

Fine needle aspiration (FNA) cytology has become widely accepted as a reliable diagnostic tool for diagnosis breast masses. It is a simple and safe method which yields high diagnostic performances (Koss, 1993; Rubin et al., 1997; O' Neil et al., 1997; Chaiwun et al., 2002). The procedure is considered very cost effective by being less invasive, less expensive, rapid, and even more sensitive than biopsy (O' Neil et al., 1997; Rubin et al., 1997). Thus, it plays a major role as an important preoperative assessment along with clinical and mammography examination, which together are frequently referred as "Triple test" (Hermansen et al., 1987; Kaufman et al., 1994). Combination of the triple test and open surgical biopsy has been firmly established as highly accurate in the diagnosis of breast masses (Hermansen et al., 1987; Kaufman et al., 1994; Negri et al., 1994).

In 2007, Chaiwun and Thorner reviewed diagnostic performances of FNA in breast lesions; the sensitivity was in the range of 75.8-98.7%; specificity of 60-100%; positive predictive value of 93.5-100%; negative predictive value of 67-95.7%; accuracy of 72-94.8%; with false positive and false negative rates of 0-2.5% and 2.5-17.9% respectively. Another recent meta-analytical review, including 25 studies of FNA, has shown that FNA cytological analysis of palpable breast masses is highly accurate to differentiate benign from malignant tumors (Akçil et al., 2008). Although core needle biopsy is preferred over FNA in some countries, such as the United Kingdom and the United States (Britton et al., 1997; Cobb and Raza, 2005), it is still commonly used in Asia and other developing countries with low financial resources (Chaiwun et al., 2002; Chaiwun and Thorner, 2007). The aim of this study was to evaluate the diagnostic performances including the accuracy of FNA for a diagnosis of breast masses being investigated in our institution in comparison to the histopathological findings.

Department of Anatomical Pathology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, Bangkok, Thailand
**For Correspondence: siriwanonco@yahoo.com*

Materials and Methods

The study was conducted after an approval from the Ethics Committee for Research involving Human Subjects of Bangkok Metropolitan Administration (registered number 0061.50). We searched the archive of Department of Anatomical Pathology of our institution for women with breast masses, who had had FNA cytological diagnoses and histopathologic evaluation, during January 2003-December 2006. We assessed the accuracy of FNA finding by comparing the cytological diagnoses of breast masses to the diagnoses from histopathology reports, obtained with core needle biopsy, excisional biopsy, or mastectomy.

In our institution, the clinician usually performs a thorough physical examination of breasts, mammography with or without ultrasonography, and FNA to obtain a diagnosis of breast masses. The FNA was obtained through a 22-24-guage needle; the apirated content was then smeared on glass slide and fixed by 95% ethanol or was air-dried. Five slides were prepared per case. Four fixed slides were stained with Papanicolaou staining while one air-dried slide was stained with Diff-Quik. Cytological diagnoses were classified into 5 categories according to the National Cancer Institute Consensus Conference on Breast FNA (1997): unsatisfactory, benign, atypical probably benign, suspicious probably malignant, and malignant. Cases which were reported as unsatisfactory by FNA were not included for the analysis. Cases reported as atypical probably benign or suspicious probably malignant were grouped together and classified as suspicious group because these two categories were reported to have a similar probability of malignancy (Chaiwun et al., 2005).

Statistical analysis to determine sensitivity, specificity, positive predictive value, negative predictive value with their 95% confidence intervals [CI] was performed with the statistical computing programme Stata/SE 7.0 (Stata Corp., College station, TX, USA). Positive and negative predictive values were calculated with two alternatives: inclusion of only the malignant and benign FNA diagnoses (excluding the suspicious group) and of the entire group (including the suspicious group). For statistical purposes of the sensitivity of the entire group, the suspicious and malignant cases were grouped together on the assumption that the suspicious cases were positive for malignancy.

Results

During the study period, we identified 190 breast masses from190 women. All of these patients presented with self-palpable breast masses or were incidentally detected during medical examination. Median age was 46 years (range, 18-92 years). The gross pathological lesions of breast masses varied in size ranging from 0.6-10 cm (mean, 2.54 +10 cm). Out of 190 cases, eight cases (4.2%) had inadequate cellular components for cytological assessment and the unsatisfactory FNA cytological diagnoses were given. So, the statistical analysis was performed in 182 cases. Diagnoses are listed in Table 1 and the comparison results in Table 2. Table 3 summarizes data for overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value respectively. False positive and false negative rates for the entire group were 5.5% and 3.3%, respectively.

Table 1. Histopathology of Breast Masses According to the Cytologic Diagnoses (n=182)

Histopathology by category of cytology	No. of cases
Benign FNA	98 (53.9%)
Fat necrosis/ abscess/ granulomatous mastitis or chronic inflammation	7
Adenosis	2
Ductal hyperplasia	3
Intraductal papillomatosis	2
Fibrocystic disease	40
Fibroadenoma	36
Benign phylloides tumor	2
Infiltrative ductal carcinoma	6
Suspicious FNA	31 (17.0%)
Fibrocystic disease	4
Fibroadenoma	3
Intraductal papillomatosis	2
Malignant phylloides tumor	2
Mmalignant lymphoma	1
Infiltrative ductal carcinoma	19
Malignant FNA	53 (29.1 %)
Fibroadenoma	1
Infiltrative ductal carcinoma	52

Table 2. Comparison of Fine Needle Aspiration (FNA) Cytology and Histopathology Findings (N=182)

	Histopathology		
FNA	Benign	Malignant	Total
Benign	92 (93.9) (TN)	6 (6.1) (FN)	98 (100)
Suspicious	9 (29.0) (FP)	22 (71.0) (TP)	31 (100)
Malignant	1 (1.9) (FP)	52 (98.1) (TP)	53 (100)
Total	102 (100)	80 (100)	182 (100)

Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive

Table 3. Diagnostic Performance of Fine Needle Aspiration Cytology for Breast Masses (N=182)

Parameter	Value (%)	95% CIs
Accuracy	91.2	(87.6-94.8)
Sensitivity	92.5	(88.7-96.3)
Specificity	90.2	(85.9-94.5)
Positive predictive value	88.1	(83.4-92.8)
Negative predictive value	93.9	(90.4-97.4)

CIs, confidence intervals

Discussion

The results of our study showed FNA of breast masses to be a reliable method to diagnose breast mass with high accuracy and sensitivity. From the review of Chaiwun and Thorner (2007) and the recent meta-analytic review of Akçil et al. (Akçil et al., 2008), the sensitivity of FNA of breast masses ranged approximately from 76%-100% while the specificity and the accuracy were 60%- 100% and 72%– 95% respectively. The accuracy of 91.2%, sensitivity of 92.5%, and specificity of 90.2% found in our study were within the ranges as had been reported (Chaiwun and Thorner, 2007; Akçil et al., 2008).

We found 4.2% of cases in our study had inadequate mammary epithelial cells that the cytologic diagnosis could not be made. Other studies showed frequency of inadequate specimens varied tremendously from 0.7%-47% (Chaiwun et al., 2002; Chaiwun and Thorner, 2007). Some authors provided the reasons for unsatisfactory specimens (Vetto et al., 2005; Orell and Miliaushas, 2005). One was the insufficient experience of the surgeons who performed the aspirations while another possibility was the nature of the lesions themselves. For example, fatty lesions (lipoma or fat necrosis) or hypocellular lesions (which contained few cellular components) and some malignant lesions frequently had unsatisfactory cytology. Others suggested some measures to reduce the rate: the proper training of the physicians who perform the aspirates (Ljung et al., 2001; Day et al., 2008) the use of ultrasound-guided FNA (Kamphausen et al., 2003; Saravanja et al., 2005) and an immediate evaluation by a pathologist using rapid staining either Romanosky or Diff-Quick stain (Chaiwun et al., 2002; Berner et al., 2003). Our study found fewer unsatisfactory specimens compared to the other studies. This may lie with many reasons. First, we had a practice guideline of the institution that the operator performing the aspiration had to be an experienced surgeon of the Department of Surgery or the surgical resident-in training under a close supervision of the surgeons. Second, all women with mass lesions usually had undergone mammography with ultrasonography before the surgical procedure. Ultrasonographic findings were available to help the surgeon locate the actual site of a lesion. Third, the aspirations were submitted to the Anatomical Pathology Department right after the procedure.

Our study had suspicious FNA diagnoses (atypical/ suspicious aspirates) at 17%, in line with previous reports in the range of 4%-17.7% (Chaiwun et al., 2002). Our high prevalence rate of suspicious FNA might be due to the level of precaution or the preference of the pathologist in each institution. Our cytopathologist tended to give the primary cytologic diagnosis of suspicious lesion when there were some atypical cellular features but without definite evidences of malignancy. Then direct contact with the surgeon was carried out to gain more clinical information. The majority of our suspicious cases turned out to be malignant lesions from the subsequent histopathology (71%).

When the suspicious and malignant cases were grouped together, the false positive in our study were encountered in 10 cases (5.5%). Other studies reported that false positive results of FNA of breast masses are uncommon, occurring in 0-2.5% (Chaiwun et al., 2002; Chaiwun and Thorner, 2007). The differences might lie on the grouping of the suspicious cases together with or separated from malignant cases. As mentioned earlier, our study included the suspicious cases together with the malignant cases; the former group of the suspicious cytology contribute to the majority of the false positive cases (9/10 cases). When we reviewed these slides, we found that most of them were due to error in interpretation. Thus, we agree with previous studies that suspicious cases should have confirmed by histopathological examination (Kanhoush et al., 2004: Chaiwan et al., 2005). In this study, the histopathologic diagnoses of these false positive (from the suspicious cases) were fibrocystic disease (four cases), fibroadenoma (three cases), and intraductal papillomatosis (two cases). These findings were similar to prior reports that the epithelial proliferative of ductal or lobular hyperplasia often accounted for the false positive result (O'Neil et al., 1997; Orell and Farshid, 2001). This certainly emphasizes the role of experience to minimize the false positive rate. The only benign case which was interpreted as malignant was fibroadenoma, in,ine with the earlier report that cytomorphological features of fibroadenoma may overlap with other benign, proliferative and non-proliferative lesions, and malignant tumors (Benoit et al., 1992). On the other hand, the diagnosis of fibroadenoma is still considered reliable when taken other clinical data (triple test) into the appraisal together with the cyto/histopathology (Kollur et al., 2006).

The overall false negative rate in our study was 3.3 % (six cases) which was low in the range as had been reported in the other studies, 2.5-17.9% (reviewed in Chaiwun and Thorner, 2007). All false negative cases had histopathologic diagnoses of infiltrative ductal carcinoma. Factors contributing to false negative results may include: small tumor size; hypocellularity and inadequate sampling during aspiration; interpretative problems; particular histologic tumor types, such as, low nuclear grade carcinoma or scirrhous tumors (Park and Ham, 1997; Chaiwun et al., 2002). One study showed that the adequate number of epithelial clusters was an important factor which could reduce the false negative rate in breast masses by approximately 50% (Boerner and Sneige, 1998).

While the false positive results could lead to an over-treatment of an unnecessary or excessive surgery, false negative results can mislead a clinician and cause a delay in appropriate investigation, diagnoses, and treatment. Hence, FNA should not used as the sole modality and results must be interpreted in correlation with all the clinical and imaging findings (the triple test) to reduce errors and allow proper management for each patient (Kaufman et al., 1994; Negri et al., 1994; Chaiwun et al., 2005; Brenner et al., 2001).

The surgeon should be acquainted with additional techniques such as core needle biopsy or excisional biopsy in cases with a high index for suspicion for malignancy. Some authors advocated a core needle biopsy (CNB) as an alternative approach to surgically opened biopsy and stated that it was superior to FNA. This might lie on the fact that the CNB could better detect the incidence of ductal carcinoma in situ which has been increasing among all breast cancers (Litherland et al., 1996). Furthermore, CNB provides better information for its tissue histopathologic evalaution and an adequate material for ancillary studies, such as, immunohistochemical study to determine estrogen/ progesterone receptors and HER2 (Usami et al., 2007). Nevertheless, some reasons may preclude the popular use of CNB. The diagnostic performances of CNB were similar to the FNA; the sensitivity, specificity and accuracy of CNB were 91-92%, 98-100% and 96-97%, respectively (Brenner et al., 2001). Another obvious reason is because the CNB is more invasive, time – consuming, and expensive compared with

FNA.

This study indicates that FNA is a highly reliable tool in the assessment of breast masses for the differential diagnoses of benign from malignant natures. It is a simple, safe, cost-effective, and accurate method for the initial diagnosis and for guiding treatment. However, one must be aware of the possibility of false positive and false negative results. We support the standard recommendation that patients with breast masses should be diagnosed based on a combination of physical examination, radiological modalities and FNA (the "triple test").

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References

Akçil M, Karaagao_lu E, Demirhan B (2008). Diagnostic accuracy of fine-needle aspiration cytology of palpable breast masses: An SROC curve with fixed and random effects linear meta-regression models. *Diagn Cytopathol*, **36**, 303-10.

Benoit JL, Kara R, McGregor SE, Duggan MA (1992). Fibroadenoma of the breast: diagnostic pitfalls of fine-needle aspiration. *Diagn Cytopathol*, **8**, 643-8.

Berner A, Davidson B, Sigstad E, Risberg B (2003). Fine-needle aspiration cytology vs core biopsy in the diagnosis of breast lesions. *Diagn Cytopathol*, **29**, 344-8.

Boerner S, Sneige N (1998). Specimen adequacy and false-negative diagnosis rate in fine-needle aspirates of palpable breast masses. *Cancer*, **84**, 344-8.

Brenner RJ, Bassett LW, Fajardo LL, et al (2001). Stereotactic core-needle breast biopsy: a multi-institutional prospective trial. *Radiology*, **218**, 866-72.

Britton PD, Flower CD, Freeman AH, et al (1997). Changing to core biopsy in an NHS breast screening unit. *Clin Radiol*, **52**, 764-7.

Chaiwerawatana A (2007). Breast. In 'Cancer in Thailand Vol. IV, 1998-2000' , Eds Khuhaprema T, Srivatanakul P, Sriplung H, Wiangnon S, Sumitsawan Y, Attasara P. Bangkok Medical Publisher, Bangkok pp 48-50.

Chaiwun B, Settakorn J, Ya-In C, et al (2002). Effectiveness of fine-needle aspiration cytology of breast: analysis of 2,375 cases from northern Thailand. *Diagn Cytopathol*, **26**, 201-5.

Chaiwun B, Sukhamwang N, Lekawanvijit S, et al (2005). Atypical and suspicious categories in fine needle aspiration cytology of the breast: histological and mammographical correlation and clinical significance. *Singapore Med J*, **46**, 706-9.

Chaiwun B, Thorner P (2007). Fine needle aspiration for evaluation of breast masses. *Curr Opin Obstet Gynecol*, **19**, 48-55.

Cobb CJ, Raza AS (2005). Obituary: "alas poor FNA of breast-we knew thee well!". *Diagn Cytopathol*, **32**, 1-4.

Day C, Moatamed N, Fimbres AM, et al (2008). A retrospective study of the diagnostic accuracy of fine-needle aspiration for breast lesions and implications for future use. *Diagn Cytopathol*, **36**, 855-60.

Hermansen C, Skovgaard Poulsen H, Jensen J, et al (1987). Diagnostic reliability of combined physical examination, mammography, and fine-needle puncture ("triple test") in breast tumors: a prospective study. *Cancer*, **60**, 1866-71.

Kamphausen BH, Toellner T, Ruschenburg I (2003). The value of ultrasound-guided fine – needle aspiration cytology of the breast: 354 cases with cytohistological correlation. *Anticancer Res*, **23**, 3009-13.

Kanhoush R, Jorda M, Gomez-Fernandez, et al (2004). 'Atypical' and 'suspicious' diagnoses in breast aspiration cytology. *Cancer*, **102**, 164-7.

Kaufman Z, Shpitz B, Shapiro M, et al (1994). Triple approach in the diagnosis of dominant breast mass: combined physical examination, mammography, and fine-needle aspiration. J *Surg Oncol*, **56**, 254-7.

Kollur SM, El Hag IA (2006). FNA of breast fibroadenoma: observer variability and review of cytomorphology with cytohistological correlation. *Cytopathol*, **17**, 239-44.

Koss LG (1993). The palpable breast nodule: a cost effectiveness and analysis of alternate diagnostic approaches: the role of the needle aspiration biopsy. *Cancer*, **72**, 1499-502.

Litherland JC, Evans AJ, Wilson AR, et al (1996). The impact of core-biopsy on pre-operative diagnosis rate of screen detected breast cancers. *Clin Radiol*, **51**, 562-5.

Ljung BM, Drejet A, Chiampi N, et al (2001). Diagnostic accuracy of fine-needle aspiration biopsy is determined by physician training in sampling technique. *Cancer*, **93**, 263-8.

Negri S, Bonetti R, Capitanio A, Bonzanini M (1994). Preoperative diagnostic accuracy of fine-needle aspiration in the management of breast lesions: comparison of specificity and sensitivity with clinical examination, mammography, echonography, and thermography in 249 patients. *Diagn Cytopathol*, **11**, 4-8.

O' Neil S, Castelli M, Gattuso P, et al (1997). Fine-needle aspiration of 697 palpable breast lesions with histopathologic correlation. *Surgery*, **122**, 824-8.

Orell SR, Farshid G (2001). False positive reports in fine needle biopsy of breast lesions. *Pathology*, **33**, 428-36.

Orell SR, Miliaushas J (2005). Fine needle biopsy cytology of breast lesions: a review of interpretative difficulties. *Adv Anat Pathol*, **12**, 233-45.

Park IA, Ham EK (1997). Fine needle aspiration cytology of palpable breast lesions. Histologic subtype in false negative cases. *Acta Cytol*, **41**, 1131-8.

Pisini P, Parkin DM, Ferlay J (1993). Estimates of the worldwide mortality from eighteen major cancers in 1985: implications for prevention and projections of future burden. *Int J Cancer*, **55**, 891-903.

Rubin M, Horiuchi K, Joy N, et al (1997). Use of fine needle aspiration for solid breast lesions is accurate and cost-effective. *Am J Surg*, **174**, 694-8.

Saravanja S, Kubik-Huch RA, Komminoth P, et al (2005). Ultrasound-guided fine needle aspiration of the breast. *Praxis*, **94**, 673-9 (in German).

The uniform approach to breast fine-needle aspiration biopsy (1997). National Cancer Institute Fine-Needle Aspiration of Breast Workshop Subcommittees. *Diagn Cytopathol*, **16**, 295-311.

Usami S, Moriya T, Amari M, et al (2007). Reliability of prognostic factors in breast carcinoma determined by core needle biopsy. *Jpn J Clin Oncol*, **37**, 250-5.

Vetto JT, Pommier RF, Shin RL, et al (2005). Breast fine-needle aspirations with scant cellularity are clinically useful. *Am J Surg*, **189**, 621-6.