Original Article

Approach to Fine-needle Aspiration Cytology-negative Cases of Breast Cancer

Shugo Mizuno, Shuji Isaji, Tomoko Ogawa, Masami Tabata, Kentaro Yamagiwa, Hajime Yokoi and Shinji Uemoto, First Department of Surgery, Mie University School of Medicine, Mie, Japan.

OBJECTIVE: To clarify the clinical usefulness of fine-needle aspiration (FNA) cytology of breast tumours and the management of FNA cytology-negative cases suspected of or equivocal for malignancy.
METHODS: FNA cytology was performed in 94 patients between 1995 and 2002. We calculated the sensitivity, specificity and accuracy of FNA cytology for the diagnosis of malignancy. We also compared clinical and radiological findings between false-negative and true-negative cases.
RESULTS: The sensitivity of FNA was 91% (72/79), specificity was 93% (14/15), accuracy was 91% (86/94), positive predictive value was 99% (72/73) and negative predictive value was 67% (14/21). There were seven false-negative cases and one false-positive case. Findings that aroused suspicion of malignancy were more frequent in the false-negative cases, especially from mammography and magnetic resonance imaging (MRI).
CONCLUSION: FNA cytology was an accurate preoperative diagnostic procedure for the evaluation of breast masses. In FNA cytology-negative cases, repeated FNA, core needle biopsy or excisional biopsy needs to be performed based on MRI findings. [*Asian J Surg* 2005;28(1):13–7]

Key Words: fine-needle aspiration biopsy, breast cancer, FNA cytology-negative case

Introduction

Triple assessment, consisting of clinical evaluation, mammography or ultrasound, and fine-needle aspiration (FNA) cytology, allows precise initial diagnosis of palpable breast masses and reduces the risk of misdiagnosis.[1] FNA cytology is usually performed on palpable breast masses, especially in cases suspected of malignancy, and positive cytology is considered sufficient evidence for a diagnosis of breast cancer. Such cases can then be treated using mastectomy or breast-conserving surgery without the need for a time-consuming tumour biopsy.

However, because there are false-negative cases, attributable to a variety of factors besides technical failure, the diagnostic accuracy of FNA biopsy for breast cancer is only around 95%. The treatment of FNA cytology-negative patients who are otherwise suspected of having malignant breast cancer based on physical and/or breast imaging findings, or in whom such findings are equivocal, presents a dilemma. Since several studies have shown that delay in the diagnosis of breast cancer reduces survival,[2,3] early definitive diagnosis of breast masses is important in FNA cytology-negative cases.

Core needle biopsy (CNB), on the other hand, is thought to provide a more exact diagnosis of breast tumours,[4] especially non-palpable breast tumours. However, CNB is not widely used in some medical centres, especially in Asian countries, because it takes more time, often necessitates anaesthesia, and requires many staff members who are familiar with certain techniques. As a result, it is sometimes difficult to decide on the next step, that is, whether to perform a CNB, a lumpectomy or more extensive surgery.

In this study, we assessed the clinical usefulness of FNA biopsy of breast tumours in the preoperative diagnosis

Address correspondence and reprint requests to Dr. Shugo Mizuno, First Department of Surgery, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie, Japan.
E-mail: mizuamido@mtj.biglobe.ne.jp • Date of acceptance: 28 January 2004

of breast cancer and carefully reviewed the FNA cytology-negative cases.

Materials and methods

The subjects in the present study were among 94 patients who underwent FNA cytology of palpable breast masses in the First Department of Surgery, Mie University Hospital, between January 1995 and December 2002. Their ages ranged from 25 to 78 years (mean, 51 years). Informed consent was obtained from every patient before cytology. There were no major complications or significant complaints of pain. FNA cytology was followed by lumpectomy or mastectomy, and a histological diagnosis was made in every patient.

The technique of FNA has been described previously.[5] Briefly, aspirates were obtained with a 22 gauge needle and a 20 mL syringe, and the needle was guided by ultrasound (US) whenever the tumour was smaller than 2 cm. At least two aspirates were collected each time FNA was performed, and direct smears were prepared for cytology. Alcohol-fixed smears were stained with Papanicolaou stain. Unsatisfactory smears were excluded and repeat FNA cytology was performed shortly thereafter. The diagnostic FNA cytology classification was: class I, benign; class II, probably benign; class III, equivocal; class IV, probably malignant; and class V, malignant. The definition of "cytological malignancy", or possible malignancy, comprised classes III, IV and V. The sensitivity, specificity and accuracy of FNA biopsy for the diagnosis of malignancy were calculated.

The physical examination findings and the ultrasonography, mammography and magnetic resonance imaging (MRI) findings were reviewed in FNA cytology-negative cases in an attempt to identify clinical and radiological findings that were helpful in managing FNA cytology-negative cases. Lesions were suspected of being malignant whenever any of the following findings were present: skin dimpling on physical examination, irregular-shaped mass with or without posterior echo attenuation on ultrasonography, category 3 or more on mammography, and early enhancement on a dynamic MRI study.

Statistical analysis

Comparisons between the two groups were made using the Chi-squared test for discrete variables. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc, Chicago, IL, USA) and p values less than 0.05 were considered statistically significant.

Results

Accuracy of FNA biopsy

The relationship between FNA cytology and the histopathological findings is shown in Table 1. Evaluation of the accuracy of FNA biopsy yielded a sensitivity of 91% (72/79), specificity of 93% (14/15) and accuracy of 91% (86/94). FNA biopsy had a positive predictive value of 99% (72/73) and a negative predictive value of 67% (14/21). Seven false-negative cases (class I, 1; class II, 6) and one false-positive case (class IV, 1) were identified.

Final histopathological diagnosis according to FNA cytology findings

Table 2 shows the final histopathological diagnoses of the breast masses according to the preoperative cytology class. The seven false-negative biopsy specimens were obtained from three cases of scirrhous carcinoma, three cases of papillotubular carcinoma and one case of mucinous carcinoma. Of the 15 benign cases, nine were fibroadenomas, five were fibrocystic disease and one was a cyst. Cytology was class IV in one of the benign cases, but excisional biopsy revealed fibrocystic disease.

Triple assessment of breast masses in FNA cytology-negative cases

Table 3 shows the background and results of imaging studies in the 21 FNA cytology-negative cases. Mean age and mean tumour diameter were not significantly different. The physical findings suggested malignancy in six malignant and nine benign cases, while US findings suggested malignancy in six malignant and seven benign cases. In contrast, the proportion of cases in which mammography findings were suggestive of malignancy was much higher among malignant cases than benign cases (5/7 vs 5/14). Moreover, although the number of cases was small, MRI showed evidence of malignancy in all

Table 1. Fine-needle aspiration cytology and histological findings in the diagnosis of breast masses

	Malignant (n = 79)	Benign (n = 15)	Total (n = 94)
Class I	1	2	3
Class II	6	12	18
Class III	7	0	7
Class IV	13	1	14
Class V	52	0	52

Table 2. Histological diagnoses of breast masses according to cytology findings

	Malignant (*n* = 79)				Benign (*n* = 15)		
	Scirrhous	Papillotubular	Solid-tubular	Others	Fibroadenoma	Fibrocystic disease	Cyst
Class I	1	0	0	0	1	1	0
Class II	2	3	0	1*	8	3	1
Class III	3	1	3	0	0	0	0
Class IV	4	6	3	0	0	1	0
Class V	19	17	13	3†	0	0	0
Total	29	27	19	4	9	5	1

*Mucinous; †mucinous, medullary and pagetoid.

Table 3. Triple assessment of breast masses in fine-needle aspiration (FNA) cytology-negative cases

Histological diagnosis	Mean age (yr)	Mean size (cm)	First FNA	Physical examination	Malignant findings		
					US	Mammogram	MRI
Malignant (*n* = 7)*	52	2.0	Class I (*n* = 1), class II (*n* = 6)	6/7	6/7	5/7	3/3
Benign (*n* = 14)†	55	2.3	Class I (*n* = 2), class II (*n* = 12)	9/14	7/14	5/14	0/2

*Invasive ductal carcinoma (*n* = 6) and mucinous carcinoma (*n* = 1); †fibroadenoma (*n* = 9), mastopathy (*n* = 4) and cyst (*n* = 1).
US = ultrasound; MRI = magnetic resonance imaging.

three malignant cases, while no findings of malignancy were observed in the benign cases.

FNA cytology-false-negative cases

The clinicopathological characteristics of the seven false-negative cases are shown in Table 4. All seven patients were re-examined by FNA biopsy. Cases 1 and 4 were diagnosed as breast cancer (class V), while class II or III cytology findings were demonstrated in the other five cases. Lumpectomy (tumour resection with a minimal cancer-free margin) or wide excision (tumour resection with a cancer-free margin of at least 1 cm) was performed within 1 week because of strong suspicion of malignancy based on the physical and imaging findings.

Class III cases

The FNA cytology was class III in seven cases, and repeat FNA biopsy was performed within a week in all cases. Based on the second FNA cytology, six cases were diagnosed as breast cancer (class V, 1; class IV, 5). The other case was again diagnosed as class III, and lumpectomy was performed 1 week later because the tumour was 1.5 cm in diameter. The histological diagnosis was scirrhous carcinoma and breast-conserving surgery was carried out.

Table 4. Clinicopathological characteristic of fine-needle aspiration (FNA) biopsy false-negative cases

Case	Age (yr)	Size (cm)	First FNA	Method of definitive diagnosis	Operation	Histological diagnosis	Stage
1	36	4.0	Class I	Repeat FNA (Class V)	Brt + Mn + Ax	Scirrhous carcinoma	II
2	71	3.5	Class II	Wide excision	Bp	Papillotubular carcinoma*	I
3	46	2.5	Class II	Wide excision	Bp + Ax	Mucinous carcinoma	I
4	51	2.0	Class II	Repeat FNA (Class V)	Brt + Ax	Scirrhous carcinoma	I
5	53	2.0	Class II	Lumpectomy	Brt + Ax	Papillotubular carcinoma	II
6	51	1.5	Class II	Lumpectomy	Bp + Ax	Papillotubular carcinoma*	I
7	57	1.0	Class II	Lumpectomy	Bp + Ax	Scirrhous carcinoma*	I

*Including cystic change. Brt = mastectomy; Mn = resection of minor pectoral muscle; Ax = dissection of axillary lymph node; Bp = partial mastectomy.

Discussion

The first step in the management of every patient presenting with a palpable breast mass after clinical evaluation is assessment consisting of clinical evaluation, mammography or ultrasound, and FNA cytology. These allow precise initial diagnosis of palpable breast tumours and reduce the risk of misdiagnosis.[1] FNA biopsy can be performed in an outpatient department because there are no absolute contraindications and no major complications associated with the procedure. FNA of the breast is a safe, reliable and minimally invasive biopsy technique. This method has been found to be very accurate for diagnosis of breast cancer in our hospital, with a sensitivity of 91%, specificity of 93%, accuracy of 91%, and a positive predictive value of 99%. However, with a negative predictive value of only 67%, we focused on FNA cytology-negative cases and how to treat them. Most authors have reported sensitivities, specificities and accuracies of more than 90% (Table 5).[6–8] However, negative predictive values were worse in all reports.

False-negative cases invariably occur and lessen the usefulness of FNA cytology. Several studies have examined the approach to FNA-negative cases. Tsukamoto et al pointed out that diagnostic accuracy varies significantly with the skill of the cytologist and/or aspirator.[9] Jenner et al indicated that triple assessment, consisting of clinical examination, radiographic assessment by mammography and cytological assessment using FNA cytology, is not sensitive enough to detect every breast cancer and that a high incidence of diagnostic delay is therefore inevitable with the biopsy and cytodiagnostic techniques currently available.[10] To increase the accuracy of FNA biopsy, cytologists and aspirators should review the results of every FNA biopsy to improve their skill.

Recent reports describe various advanced biopsy devices and methods of diagnosis designed to allow earlier and more accurate diagnosis of breast cancer. Schwartzberg et al indicated that advanced breast biopsy instrumentation, including stereotactic and ultrasonography-guided automated 14-gauge needle core biopsy, stereotactic vacuum-assisted core biopsy and needle localization excisional breast biopsy, are safe, reliable and minimally invasive, making these techniques very useful, especially in patients with abnormal mammographic findings but no palpable lesions.[11] In addition, Tsukamoto and coworkers reported that the diagnostic accuracy of fluorescence *in situ* hybridization (FISH) of FNA samples is comparable to that of conventional cytology and that FISH is useful in making a definitive diagnosis of malignancy in patients with indeterminate cytology findings.[9]

In our institution, stereotactic core biopsy has been used to diagnose some breast masses since 2001. All were diagnosed as breast cancer and all results were confirmed. However, in any institution, it takes time to become familiar with core biopsy techniques before this can be used with certainty as a reliable method of diagnosis.

There is a consensus that a delay of more than 6 months in the diagnosis of breast cancer is associated with a lower survival rate.[12] A recent systematic review of the literature attempted to correct for lead-time bias.[13] The authors suggested that a delay of more than 3 months may significantly reduce survival time. The problem, therefore, seems to be how to deal with negative cases according to FNA biopsy results. Apantaku suggests that FNA biopsy should be used as the initial diagnostic test, and that if needle cytology and imaging studies are negative, the mass should be closely monitored by a repeat physical examination in 2 months and repeat imaging in 6 months.[14] Lumpectomy might be recommended instead of FNA cytology when a mass is suspected of being malignant clinically.[14] Accordingly, in the present study, we reviewed the 21 FNA cytology-negative cases on the basis that evidence of the presence or absence of malignancy was frequently detected on physical examination and imaging studies. Physical examinations and US studies were poor means of differentiating between benign and malignant lesions, whereas evidence of malignancy was frequently detected by mammography and MRI. The ability of MRI to differentiate between benign and malignant disease was particularly high. The International

Table 5. Reports showing fine-needle aspiration results

Report	Sensitivity, %	Specificity, %	Accuracy, %	Positive predictive value, %	Negative predictive value, %
Ayata et al[6]	99	99	99	100	96
Ariga et al[7]	98	98	98	99	91
Chaiwun et al[8]	84	99	91	99	84
Present study	91	93	91	99	67

Breast Cancer Consensus Conference concluded that MRI is a promising technology with the potential to solve many breast cancer management problems and that it is helpful in preoperative evaluation of the extent of local tumours.[15] MRI has also recently been found to be useful in detecting intraductal spread and estimating the extent of breast cancer.[16]

The following protocol is used in our clinic to diagnose and treat FNA cytology-negative cases (class I or II) in which a malignant breast tumour is suspected based on physical and imaging findings, especially from MRI (Figure). If FNA is negative but US or mammography indicates malignancy, we perform MRI. Recently, using MRI, most cases have been diagnosed as various histological types, such as solid-tubular, mucinous, papillotubular, scirrhous carcinoma or papillary and cystic lesions. If a solid-tubular or mucinous carcinoma is suspected from MRI, we perform repeat FNA, because these types are thought to be easy to diagnose by FNA, and most false-negatives are caused by technical failure. If papillotubular carcinoma or scirrhous carcinoma is suspected from MRI, we perform CNB, because these types are not as easily diagnosed by FNA as solid-tubular or mucinous carcinoma. If a papillary or cystic lesion is suspected from MRI, we perform excisional biopsy because these types may be difficult to diagnose precisely even by CNB.

The handling of class III cases has been controversial because class III means suspicion of malignancy. We perform MRI in most class III cases and follow the protocol shown in the Figure.

We conclude that aspiration cytology is an accurate preoperative diagnostic procedure for the evaluation of breast masses, and that whenever there is clinical or radiological suspicion of malignancy, in negative FNA cases based on MRI findings, repeat FNA, CNB or excisional biopsy needs to be performed.

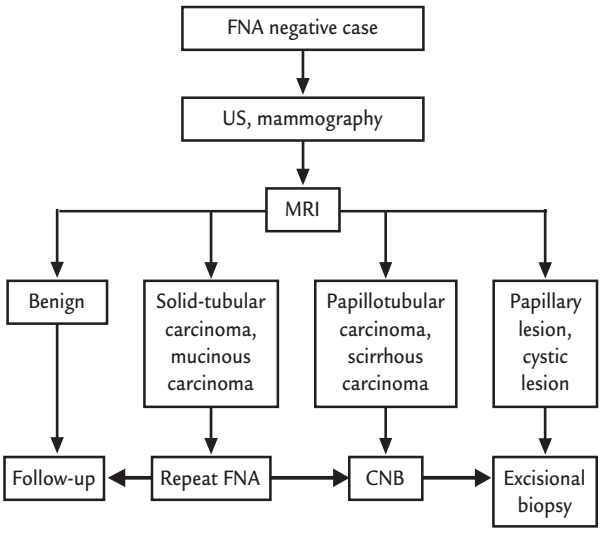

Figure. Algorithm of approach to fine-needle aspiration (FNA) cytology-negative cases. US = ultrasound; MRI = magnetic resonance imaging; CNB = core needle biopsy.

References

1. Arisio R, Cuccorese C, Accinelli G, et al. Role of fine needle aspiration biopsy in breast lesions: analysis of a series of 4,100 cases. *Diagn Cytopathol* 1998;18:462–7.
2. Neale AV, Tilley BC, Vernon SW. Marital status, delay in seeking treatment and survival from breast cancer. *Soc Sci Med* 1986;23:305–12.
3. Delgado DJ, Lin WY, Coffey M. The role of Hispanic race/ethnicity and poverty in breast cancer survival. *P R Health Sci J* 1995;14:103–16.
4. Westenend PJ, Sever AR, Beekman-De Volder HJ, et al. A comparison of aspiration cytology and core needle biopsy in the evaluation of breast lesions. *Cancer Cytopathol* 2001;93:146–50.
5. Ichikawa D, Hashimoto N, Hoshima M, et al. Analysis of numerical aberrations of specific chromosomes by fluorescent in situ hybridization as a diagnostic tool in breast cancer. *Cancer* 1996;77:2064–9.
6. 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;47:973–8.
7. Ariga R, Bloom K, Reddy VB, et al. Fine-needle aspiration of clinically suspicious palpable breast masses with histopathologic correlation. *Am J Surg* 2002;184:410–3.
8. Chaiwun B, Settakorn J, Ya-In C, et al. Effectiveness of fine-needle aspiration cytology of breast: analysis of 2,375 cases from northern Thailand. *Diagn Cytopathol* 2002;26:201–5.
9. Tsukamoto F, Miyoshi Y, Koyama H, et al. Detection of chromosomal aneusomy by fluorescence in situ hybridization in fine-needle aspirates from breast tumors: application to the preoperative diagnosis of breast carcinoma. *Cancer* 2000;90:373–8.
10. Jenner DC, Webb WM, Oommen R, et al. In-hospital delay in the diagnosis of breast cancer. *Br J Surg* 2000;87:914–9.
11. Schwartzberg BS, Goates JJ, Keeler SA, et al. Use of advanced breast biopsy instrumentation while performing stereotactic breast biopsies: review of 150 consecutive biopsies. *J Am Coll Surg* 2000;191:9–15.
12. NHS Executive. *Guidance for Purchasers. Improving Outcome in Breast Cancer: The Research Evidence.* London: Department of Health, 1996.
13. Richards MA, Westcombe AM, Love SB, et al. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999;353:1119–26.
14. Apantaku LM. Breast cancer diagnosis and screening. *Am Fam Physician* 2000;62:596–602.
15. International Breast Consensus Conference. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg* 2001;193:297–302.
16. Haramatsu H, Enomoto K, Ikeda T, et al. The role of contrast-enhanced high resolution MRI in the surgical planning of breast cancer. *Breast Cancer* 1997;25:285–90.